Mood Disorders and Addiction

8

Marta Torrens and Paola Rossi

Contents

Abstract

Comorbidity of mood and substance use disorders is the most common dual pathologies in the substance abuse field. High prevalence rates and challenging clinical management of patients diagnosed with this dual disorder imply a great burden for health care systems. Major Depression has been studied in comorbidity with the different drugs of abuse (e.g., alcohol, nicotine, cocaine, heroin, cannabis) with consistent findings throughout the world. Various neurobiological mechanisms are believed to play a role in the etiology of this comorbidity, often

M. Torrens (✉)
Institute of Neuropsychiatry and Addiction, Hospital del Mar, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

Department of Psychiatry, Universitat Autònoma de Barcelona, Barcelona, Spain
e-mail: MTorrens@parcdesalutmar.cat; mtorrens@imim.es

P. Rossi
Institute of Neuropsychiatry and Addiction, Hospital del Mar, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

G. Dom, F. Moggi (eds.), *Co-occurring Addictive and Psychiatric Disorders*,
DOI 10.1007/978-3-642-45375-5_8

determining a severe clinical phenotype with poorer prognosis when compared to addiction and mood disorders only. Treatment of the co-occurrence of depression and substance use disorder involves an integrated approach, simultaneously addressing both the psychiatric and the addictive disorder. Current research into pharmacological—in particular antidepressant drugs—and psychosocial treatments has provided controversial results. More data are needed to develop stronger evidence for the treatment of comorbid major depression and substance use disorders.

8.1 Introduction

The coexistence of Mood and Substance Use Disorders (SUD) is a fairly common occurrence. It has aroused growing interest among the scientific community due to both its high prevalence rates and the challenging clinical management of its patients. Despite the burden that SUD and mood disorders represent for clinicians and health care providers, to date, there are relatively few evidence-based data concerning such a complex comorbidity. Prevalence rates and clinical characteristics are consistent throughout different countries and cultures, despite the heterogeneity of the environmental factors involved. This chapter will focus on one of the most common mood disorders, Major Depression (MD), comorbid with substance addiction disorders.

8.2 Epidemiology

Comorbidity of MD and SUD encompasses values from 12 % to 80 % (Compton et al. 2007; Conner et al. 2008a, b, 2009; Torrens et al. 2011a). This wide range depends on a number of factors, including the sample recruitment characteristics such as general population, patients in a primary care setting, patients being treated in a psychiatric or addiction facilities, substance users not seeking treatment (e.g., in the street or prison), and even the main drug of abuse considered (e.g., opioids, alcohol, and cocaine). All these cases provide different results for prevalence, incidence, and severity indices. Moreover, variations may be related to trends in the drug-using population, such as changes in the availability, accessibility, and price of the different substances (e.g., tobacco, alcohol, cocaine, cannabis, and heroin) and drug treatment policies (e.g., accessibility to drug abuse and mental health disorder treatment) or the presence of other concurrent conditions (e.g., HIV or HCV infections), which may also be related to psychiatric comorbidity. Finally, methodological differences such as the diagnostic criteria used (Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases Diagnostic Criteria [ICD], in their different versions), the diagnostic instruments employed (e.g., the Structured Clinical Interview (SCID), the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), and the Psychiatric Research

Interview for Substance and Mental Disorders (PRISM)), and the period of time assessed (e.g., last month, last year, lifetime) may modify the figures of prevalence and incidence.

The *PsycoBarcelona* study included a population of more than 600 illicit drug users both seeking treatment in drug abuse facilities or non-seeking treatment (assessed in epidemiological research units). They were evaluated over the same period of time and in the same city (exactly similar availability, accessibility, and price of the different substances and drug treatment policies) using identical diagnostic criteria and instruments. An almost 42 % lifetime prevalence of Axis I non-SUD diagnosis was reported. The most prevalent diagnosis was independent MD (17 %) while induced MD accounted for 10 %. The drug use assessment in the study indicated that more than half the sample (from 51 % to 96 % depending on the population studied) was actively consuming more than one substance, excluding nicotine (Torrens et al. 2011a).

Worldwide, alcohol and tobacco are the most commonly used drugs. The current prevalence of alcohol use disorders in the general population ranges from almost 2 % to more than 4 %, while lifetime prevalence of alcohol dependence and abuse reaches more than 13 %. Comorbidity of alcohol dependence and MD shows a lifetime prevalence as high as 21 % (Hasin et al. 2007). Concurring data were found in a Dutch cohort of patients where comorbidity of alcohol and depression rose to 20 % (Boschloo et al. 2011). Data suggest that the presence of either alcohol abuse or MD doubles the risk of developing the other disorder (Boden and Fergusson 2011) and increases severity. The comorbidity of MD and alcohol dependence is associated with a higher risk of suicide in depressed patients; in addition, alcohol addiction has been identified as one of the strongest predictors of a repeated suicide attempt (Beghi et al. 2013).

The impact of psychiatric comorbidity has also been investigated in heroin-dependent patients. Major depression was again the most prevalent Axis I diagnosis with a prevalence ranging from 18 % to 46 % in different samples (Rodriguez-Llera et al. 2006; Astals et al. 2008; Maremmani et al. 2011),

In cocaine users, Spanish studies have reported a prevalence rate of comorbid MD (both independent or induced) disorders from 16 % in sample of outpatients to 34 % in individuals admitted to a therapeutic community (Araos et al. 2013; Herrero et al. 2008; Vergara-Moragues et al. 2012).

Within samples of cannabis-dependent subjects, figures of MD comorbidity range from 13.5 % to 38 % (Cuenca-Royo et al. 2013; Guillem et al. 2009). In the study of Cuenca-Royo et al. (2013), 18 % of regular cannabis users, assessed in nonclinical settings, presented some Axis I diagnosis other than SUD, mood disorders being the most prevalent (13.5 %). Cannabis use associated with alcohol consumption at an early age correlates with the presence of a comorbid psychiatric disorder. In addition, more severe cannabis dependence measured as the number of joints per month is related to comorbidity with both SUD and non-SUD diagnosis. With other less commonly used drugs such as ecstasy or amphetamine, the more frequent psychiatric comorbid disorder is MD (Martin-Santos et al. 2010; Salo et al. 2011). Table 8.1 summarizes some of the studies performed within the European Union about the lifetime prevalence of MD among different substance abusers assessed in various contexts.

Table 8.1 Lifetime prevalence of MD among different substance abusers, assessed in various contexts in different studies in European countries

Study	Subjects	Main drug of abuse	Sample	Diagnosis criteria	Diagnostic instrument	Lifetime prevalence of MD		
						Any (%)	Primary (%)	Induced (%)
Boschloo et al. (2011)	2,329	Alcohol	Netherlands Study of Depression and Anxiety (NESDA) cohort	DSM IV	CIDI	16.5	–	–
Rodriguez-Llera et al. (2006)	149	Heroin	Non-treatment-seeking users	DSM IV	PRISM	26.8	17.4	9.4
Astals et al. (2008)	189	Heroin	Treatment-seeking users	DSM IV	PRISM	18	12.7	5.3
Maremmani et al. (2011)	1,090	Heroin	Treatment-seeking users	DSM IV	DAH-RS (substance use) Decision Trees for Differential Diagnosis + SID	55.8 (11.8 undetermined)	25.1	18.9
Herrero et al. (2008)	139	Cocaine	Non-treatment-seeking users	DSM IV	PRISM	30.2	19.4	10.8
Araos et al. (2013)	110	Cocaine	Treatment-seeking users	DSM IV	PRISM	40.9	16.4	24.5
Cuenca-Royo et al. (2013)	289	Cannabis	General population	DSM IV	PRISM	17	13.5	3.5
Martin-Santos et al. (2010)	37	Ecstasy	Non-treatment-seeking users	DSM IV	PRISM	40.5	13.5	27

DSM IV Diagnostic and Statistic Manual of Mental Disorder IV edition, *PRISM* Psychiatric Research Interview for Substance and Mental Disorders, *DAHRS* Drug Addiction History Rating Scale, *SID* Semi-structured Interview for Depression, *CIDI* Composite International Diagnostic Interview

Interest is growing with respect to the relationship between nicotine dependence and psychiatric comorbidity. Patients affected by a depressive disorder have been described as having twice the probability to be also nicotine dependent (Hughes and Hatsukami 1992; Mendelsohn 2012). As much as 30 % of those with at least one previous depressive episode are active smokers (Cappelleri et al. 2005; Mendelsohn 2012). Furthermore, people with nicotine dependence have a higher risk (from a two- to threefold increase) of developing a mood disorder as compared to nonsmokers (John et al. 2004).

Studies carried out in both general and clinical populations indicate that women with SUD present comorbid MD more frequently than men. Moreover, in women with SUD the prevalence of MD is twice as usually found in a general European female population which makes them an especially vulnerable collective and a particularly sensitive target for treatment policies (Torrens et al. 2011a).

8.3 Etiology

Different hypothesis have been proposed to explain such a high joint occurrence of SUD and MD. In brief: (1) SUD and comorbid MD share common risk factor disorders such as stressful events, psychological trauma, genetic vulnerability, and/or similar preexisting neurobiological alterations that lead to co-occurring expression, without one disorder causing the other; (2) continued use of substances induces neurobiological changes through neuro-adaptative mechanisms that mediate MD; (3) SUD is developed in order to soothe MD symptoms (self-medication hypothesis); and (4) there are common symptoms between addiction and mood disorders which can be mistakenly diagnosed as a co-occurring MD (Schuckit 2006).

For both MD and SUD genetic and environmental factors are crucial in the induction of the neurobiological mechanisms related to their pathogenesis (Brady and Sinha 2005; Schuckit 2006). The principal neuronal and molecular mechanisms involved in the neurobiology of depression include (1) monoaminergic neurotransmission systems; (2) hypothalamus–pituitary axis (HHA); (3) immunological system; (4) neurotrophic factors (e.g., BDNF, Brain-Derived Neurotrophic Factor); (5) endocannabinoid system; and (6) food intake, metabolism, and circadian rhythm control system (Belmaker and Agam 2008; Krishnan and Nestler 2008; Valverde et al. 2009; Valverde and Torrens 2012). Some of these mechanisms involved in MD also play a role in SUD (Brady and Sinha 2005). Moreover, reward circuits, one of the most important pathways in SUD (Wise 1989), have also been hypothesized as being implicated in the neurobiology of depressive disorders (Nestler and Carlezon 2006).

8.4 Clinical Characteristics

8.4.1 Diagnosis

As previously described, the clinical identification of MD in substance abusers constitutes a challenge for both medical care and research. Firstly, acute or chronic effects of substance use can mimic MD symptoms, making it difficult to differentiate the psychiatric symptoms that represent an independent (primary) MD from those related to an acute or chronic substance use or withdrawal. Furthermore, psychiatric diagnoses such as MD are syndromes rather than diseases with well-known pathophysiology and associated biological markers. The lack of biological markers has forced psychiatrists to develop operational diagnostic criteria, including the DSM and the ICD, and to design structured clinical diagnostic interviews in order to improve the validity and reliability of diagnoses. The use of standard criteria based on directly observable behavioral symptoms, and the incorporation of these into structured interviews, maximizes the extent to which identical information can be elicited and applied to the same criteria to achieve diagnosis. As mentioned before, methodological differences, particularly regarding the diagnostic criteria (e.g., DSM-III-R, DSM-IV, ICD-9, ICD-10) and assessment instruments used (e.g., the Structured Clinical Interview for DSM Disorders, SCID, the Psychiatric Research Interview for Substance and Mental Disorders, PRISM, and the Schedules for Clinical Assessment in Neuropsychiatry, SCAN), can also influence the prevalence rates of dual disorders (Torrens et al. 2006).

Among the assessment instruments available, the PRISM (Hasin et al. 2006) is a semi-structured interview that facilitates the distinction among independent (primary) disorder, substance-induced disorder, and the expected effects of the substance. The PRISM interview has demonstrated good psychometric properties in terms of test—retest reliability (Hasin et al. 2006), inter-rater reliability (Morgello et al. 2006), and validity (Torrens et al. 2004) to diagnose psychiatric disorders among substance users. That is to say, it is able to discern among *MD independent from substance* (when symptoms are substantially in excess of what would be expected given the type or the amount of the substance used or the duration of use; the onset of depressive symptoms precedes the onset of the substance use; or the symptoms persist for a period of time after the cessation of intoxication or acute withdrawal); *substance-induced MD* (when the episode occurs entirely during a period of heavy substance use or within the first 4 weeks after cessation of use, and the substance used is relevant to the disorder and the symptoms are greater than the expected effects of intoxication and/or withdrawal); and the *expected effects* (expected physiological effects of a substance, as a result of intoxication or withdrawal—e.g., insomnia—which may be identical to symptoms found in independent MD).

Distinguishing between independent and induced MD in a patient with a substance use disorder represents a challenge; nevertheless, we are able to highlight a few differential characteristics of the two forms that may be of help in clinical practice. On the one hand, a sudden change, either an increase or reduction in substance intake in the SUD, prior to the onset of depressive symptoms may indicate that the mood disorder was induced by the SUD. On the other hand,

Table 8.2 Clinical indicators for the diagnosis of a depressive episode concurrent with substance use disorder

Induced depression	Independent depression
• Emergence of depressive symptoms during an escalation of consumption • Emergence of depressive symptoms during a significant drop in consumption	• Emergence of depressive symptoms during a period of stable or occasional consumption • Persistence of depressive symptoms after one week of withdrawal • History of depression in the absence of substance use • Family history of depression. • History of good response to antidepressant treatments in the past

emergence of depressive symptoms during a period of stable consumption, or the persistence of depressive symptoms after clinically relevant withdrawal, probably suggests an independent MD disorder. Furthermore, in the absence of substance use, the presence of a previous history of depression or familial antecedents may indicate the existence of MD. In addition, patients with independent MD are more likely to have a history of good response to antidepressant treatments (Table 8.2). Some patients can present both independent and induced MD and undergo an increasing number of depressive symptoms throughout their lives. They are more frequently found with comorbid anxiety disorders, and are more likely to have attempted suicide (Torrens et al. 2011b).

8.4.2 Course and Prognosis

It is important to highlight that the studies that distinguish between independent and induced MD have found a clearly higher prevalence of independent MD (Torrens et al. 2011a). Furthermore, recent data from one of the most representative epidemiological study in the United States, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), are shedding light on a new perspective with respect to substance dependence and comorbid MD (Blanco et al. 2012). The subgroup of patients diagnosed at an earlier stage with induced MD or dysthymia together with SUD, when reevaluated at a second time point 3 years later, were reclassified as being affected by independent MD. Also, in a follow-up study of a Spanish cohort of ecstasy users, most of the induced MD diagnosed at the baseline t of the study were diagnosed as independent MD at a 3-year follow-up (Martin-Santos et al. 2010). This may have been due to a number of factors including a higher probability of being diagnosed with an induced affective disorder when severe drug dependence symptoms are present, or that the diagnosis of induced disorders captures subjects with a preexisting higher risk for MD whose symptoms are precipitated by substance use. It may also indicate that SUD had precipitated an MD whose erroneous diagnosis had been masked by the substance consumption (Magidson et al. 2013).

Clinical data indicate that people affected by MD present a higher vulnerability to developing a SUD, and individuals with SUD have a higher risk of developing MD when compared to the general population. Furthermore, co-occurrence of SUD and MD is a predictor of clinical severity: patients show a more severe clinical course, less response to treatment, and a poorer prognosis for both disorders overall (Boschloo et al. 2013; Conner et al. 2012; Samet et al. 2013). These dually diagnosed patients additionally present a higher prevalence of attempted/completed suicide than those with only one disorder (Conner et al. 2012; Marmorstein 2011; Blanco et al. 2012).

Besides MD, patients with comorbid SUD often manifest or develop other medical, psychiatric, and substance use comorbidities, thus making treatment even more challenging. As expected from such a severe clinical picture, dual disorder patients have considerable psychosocial disability and require an increased utilization of health care resources, including emergency rooms and psychiatric hospitalization (Mueller et al. 1994; Martín-Santos et al. 2006; Pettinati et al. 2013; Samet et al. 2013).

8.5 Treatment

Given its psychopathological, medical, and social severity and relevance in prognosis, adequate treatment for comorbid MD and SUD is needed. However, in spite of the high association between substance use and MD, there is a surprising paucity of studies related to treatment and outcome. A few well-designed studies, mainly concerning MD comorbid with alcohol dependence, have been published, and more work of this nature is required in order to address the challenges of dual disorder treatment. A summary of the available evidence about current status of the clinical management of MD in patients with SUD is presented.

8.5.1 Pharmacological Treatment

The main results coming from the systematic reviews and meta-analyses of comorbid MD and SUD randomized clinical trials (Nunes and Levin 2004; Torrens et al. 2005; Pani et al. 2010) indicate that (1) antidepressant drugs improve comorbid depression with alcohol dependence but not the depression that concurrently occurs with cocaine or opiate dependence. Furthermore, the improvement of depression, together with alcohol dependence, takes place only with imipramine, desipramine, and nefazodone; while selective inhibitors of serotonin reuptake (SSRIs) are not effective, (2) treating depressed substance-dependent patients with antidepressants does not directly improve substance use. When the antidepressants improve depressive symptoms, there is also a quantitative reduction in the use of the substance of abuse, but no effect on the acquisition of abstinence or total remission of these substances use. Thus a specific and concomitant treatment for SUD is required. In a recent trial for comorbid MD and alcohol dependence, a combined treatment of a medication for depression (sertraline) and another for alcohol dependence (naltrexone) was found to simultaneously reduce depressive symptoms and excessive drinking (Pettinati et al. 2010).

An additional concern when treating these dual disorder patients is the safety of the treatment itself due to the frequency of comorbid physical illness (e.g., HIV and/or HVC infections, hepatic cirrhosis) and the risk of interactions with other drugs that the person may be taking (e.g., risk of QTc prolongation in HIV-infected patient receiving methadone maintenance treatment and SSRI) (Funk and Bostwick 2013; Vallecillo et al. 2013). The main interactions and general recommendations about the clinical management of patients with MD and SUD are summarized in Table 8.3. Besides aspects of efficacy, safety of antidepressant use, and possible interactions with the consumption of various substances or other drugs, the

Table 8.3 Principal interactions of antidepressants with drugs used treating addiction and substances of abuse

Drug	Antidepressant	Effect
Benzodiazepines	Tricyclic	Increase plasma concentrations of *desipramine* and *imipramine*
	SSRIs	With *fluoxetine* and *fluvoxamine* decrease metabolism and increase plasma concentrations of *alprazolam* and *diazepam*
Disulfiram	Tricyclic	Increase plasma concentrations of *desipramine* and *amitriptyline* due to decrease of metabolism, neurotoxicity of the combination
	MAOI	With *tranylcypromine*, confusional psychosis with the combination
Opioids	Tricyclic	TCA + methadone correlated with ↑ overdose risk Increase of bioavailability and analgesic effect with morphine *Amitriptyline*: ↑ overdose risk with methadone. Reports of respiratory depression with buprenorphine *Desipramine*: ↑ plasma concentrations with methadone
	SSRIs	With *fluvoxamine* ↑ plasma concentrations of methadone due to ↓ elimination
	MAOI/RIMA	Increase of fatal serotonin syndrome risk with *methadone* and *buprenorphine* *Moclobemide:* ↑ effect of morphine, fentanyl, and methadone plasma concentrations
Alcohol	Tricyclic	Increased toxicity of alcohol and decreased cognitive function *Maprotiline:* risk of convulsions
	SSRIs	Increase effect of alcohol
	MAOI	Hypertensive crisis, by increased release of catecholamines. Increased sedation
	Other antidepressant	*Trazodone* and *mirtazapine:* increased sedation
Cocaine	Tricyclics and SSRIs	Reduce craving and seizure threshold Increased heart rate, diastolic pressure, and risk of arrhythmia

SSRIs selective inhibitors of serotonin reuptake, *MAOI* monoamine oxidase inhibitors, *OWS* Opiate Withdrawal Syndrome, *RIMA* reversible inhibitor of MAO-A

potential for the abuse of the different drugs used for depression treatment should also be taken into account. A review conducted by Haddad suggested that antidepressants have no potential for dependence with the exception of tranylcypromine or amineptine for their dopaminergic effects and stimulant properties (Haddad 1999).

8.5.2 Psychosocial Interventions

Cognitive behavioral therapy (CBT) is a well-established tool for the treatment of both MD and substance disorders. The combined treatment of dual disorders is still not as commonly practiced, as it should be, despite the fact that most published data and clinical experience indicate that it could be of great importance to achieve a better outcome. Nevertheless, a growing number of combined treatments for comorbid MD and SUD are available, including psychotherapeutic treatments as an adjunct or alternative to pharmacological treatment. In a recently published meta-analysis, the impact of a number of psychotherapies, such as CBT, Twelve-Step facilitation (TSF), and motivational interviewing (MI) on MD or on SUD alone, has been evaluated with controversial results. The effectiveness of psychotherapy was also investigated in dual disorders with encouraging results (Riper et al. 2014). Data about MI alone, or associated with CBT, do not show a clear superiority of one with respect to the other. The number of CBT/MI sessions was found to directly and significantly correlate with alcohol abstinence ($P < 0.001$), and nonsignificantly with MD outcome (Riper et al. 2014). The effect sizes of CBT/MI treatments, however, appeared smaller compared to the ones observed in antidepressant treatments, as reviewed by Nunes and Levin (2004). Lastly, the effects of combined CBT/MI psychotherapy were compared to treatment as usual, with no additional information about the presence and/or type of pharmacological concomitant treatment.

A different approach has been investigated by the Building Recovery by Improving Goals, Habits, and Thoughts (BRIGHT) study, a community-based effectiveness trial that compares residential substance abuse treatment with residential treatment plus CBT for depression. The treatment consists of 16 two-hour sessions of group CBT. The results demonstrated better clinical outcome, with higher adherence to treatment and an improvement in severity of depressive symptoms at a 3-month follow-up, that persisted, even if in smaller proportions, at a 6-month follow-up (Watkins et al. 2011). This contribution warrants further investigation into group CBT and its application to the broader area of community-based treatment centers, such as primary care ones.

Then, with current available evidence, it can be stated that treatment of an MD and SUD must take both disorders into account: treatment of depression cannot replace the treatment of addiction, and conversely, treatment of addiction should not replace that of depression. Also, the literature indicates that a depressive episode should be treated as such even though the patient is an active substance user and that addiction should be addressed even if the patient is currently having a

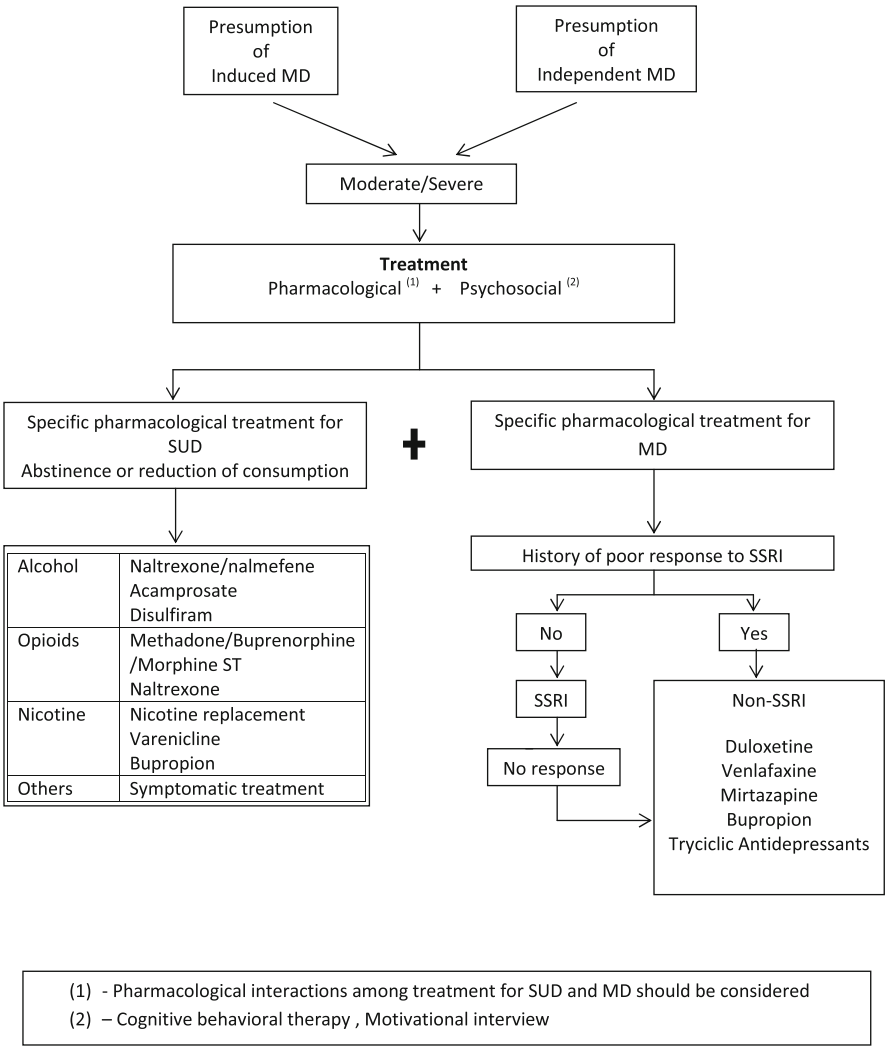

Fig. 8.1 Treatment algorithm for the management of Major Depression and Substance Use Disorder (1) Pharmacological interactions among treatment for SUD and MD should be considered (2) Cognitive behavioral therapy, Motivational interview

depressive episode. The treatment algorithm for the management of Major Depression and Substance Use Disorder is provided in Fig. 8.1.

8.5.3 Sequential, Parallel, or Integrated Treatment

It is relevant to point out that in many European countries substance abuse and mental illness are taken care of in two different and separate health networks. This implies that frequently patients with dual diagnosis are treated in separate facilities: one for drug dependence-related matters and another for psychiatric disorder ones. In many cases, abstinence from drug use is a requirement prior to the patient being admitted to treatment for depression. This attitude has now been definitively replaced by the so-called *integrated treatment* model. Such an approach embraces a simultaneous and coordinated treatment of both the addictive and the affective disorders in an effort to maximize treatment adherence and outcomes (Torrens et al. 2012).

Conclusions and Recommendations

Co-occurrence of MD and SUD is frequent, and those patients affected by dual disorders show severe psychopathological impairment as a worse medical and social outcome. It is extremely important to treat both depression and substance use disorders at the same time with an integrated model and not to approach each disorder separately following a sequential order. It is also of great priority to encourage the research of neurobiological mechanisms involved in dual disorders, in order to develop better treatments and more efficacious prevention strategies.

References

Araos P, Vergara-Moragues E, Pedraz M, Pavón FJ, Campos Cloute R, Calado M et al (2013) Psychopathological comorbidity in cocaine users in outpatient treatment. Adicciones 16(1): 15–26

Astals M, Domingo-Salvany A, Buenaventura CC, Tato J, Vazquez JM, Martin-Santos R et al (2008) Impact of substance dependence and dual diagnosis on the quality of life of heroin users seeking treatment. Subst Use Misuse 43(5):612–632

Beghi M, Rosenbaum JF, Cerri C, Cornaggia CM (2013) Risk factors for fatal and nonfatal repetition of suicide attempts: a literature review. Neuropsychiatr Dis Treat 9:1725–1736

Belmaker RH, Agam G (2008) Major depressive disorder. N Engl J Med 358(1):55–68

Blanco C, Alegria AA, Liu SM, Secades-Villa R, Sugaya L, Davies C et al (2012) Differences among major depressive disorder with and without co-occurring substance use disorders and substance-induced depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 73(6):865–873

Boden JM, Fergusson DM (2011) Alcohol and depression. Addiction 106(5):906–914

Boschloo L, Vogelzangs N, Smit JH, van den Brink W, Veltman DJ, Beekman AT et al (2011) Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders: findings from the Netherlands Study of Depression and Anxiety (NESDA). J Affect Disord 131(1–3):233–242

Boschloo L, Vogelzangs N, van den Brink W, Smit JH, Beekman AT, Penninx BW (2013) The role of negative emotionality and impulsivity in depressive/anxiety disorders and alcohol dependence. Psychol Med 43(6):1241–1253

Brady KT, Sinha R (2005) Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry 162(8):1483–1493

Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG (2005) Revealing the multidimensional framework of the Minnesota nicotine withdrawal scale. Curr Med Res Opin 21(5):749–760

Compton WM, Thomas YF, Stinson FS, Grant BF (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 64(5): 566–576

Conner KR, McCarthy MD, Bajorska A, Caine ED, Tu XM, Knox KL (2012) Mood, anxiety, and substance-use disorders and suicide risk in a military population cohort. Suicide Life Threat Behav 42(6):699–708

Conner KR, Pinquart M, Duberstein PR (2008a) Meta-analysis of depression and substance use and impairment among intravenous drug users (IDUs). Addiction 103(4):524–534

Conner KR, Pinquart M, Holbrook AP (2008b) Meta-analysis of depression and substance use and impairment among cocaine users. Drug Alcohol Depend 98(1–2):13–23

Conner KR, Pinquart M, Gamble SA (2009) Meta-analysis of depression and substance use among individuals with alcohol use disorders. J Subst Abuse Treat 37(2):127–137

Cuenca-Royo AM, Torrens M, Sanchez-Niubo A, Suelves JM, Domingo-Salvany A (2013) Psychiatric morbidity among young-adults cannabis users. Adicciones 25(1):45–53

Funk KA, Bostwick JR (2013) A comparison of the risk of QT prolongation among SSRIs. Ann Pharmacother 47(10):1330–1341

Guillem E, Pelissolo A, Vorspan F, Bouchez-Arbabzadeh S, Lepine JP (2009) Sociodemographic profiles, addictive and mental comorbidity in cannabis users in an outpatient specific setting. Encéphale 35(3):226–233

Haddad P (1999) Do antidepressants have any potential to cause addiction? J Psychopharmacol 13(3):300–307

Hasin D, Samet S, Nunes E, Meydan J, Matseoane K, Waxman R (2006) Diagnosis of comorbid psychiatric disorders in substance users assessed with the Psychiatric Research Interview for Substance and Mental Disorders for DSM-IV. Am J Psychiatry 163(4):689–696

Hasin DS, Stinson FS, Ogburn E, Grant BF (2007) Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 64(7): 830–842

Herrero MJ, Domingo-Salvany A, Torrens M, Brugal MT (2008) ITINERE Investigators. Psychiatric comorbidity in young cocaine users: induced versus independent disorders. Addiction 103(2):284–293

Hughes JR, Hatsukami DK (1992) The nicotine withdrawal syndrome: a brief review and update. Int J Smok Cessation 1:21–26

John U, Meyer C, Rumpf HJ, Hapke U (2004) Smoking, nicotine dependence and psychiatric comorbidity–a population-based study including smoking cessation after three years. Drug Alcohol Depend 76(3):287–295

Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455(7215): 894–902

Magidson JF, Wang S, Lejuez CW, Iza M, Blanco C (2013) Prospective study of substance-induced and independent major depressive disorder among individuals with substance use disorders in a nationally representative sample. Depress Anxiety 30(6):538–545

Maremmani AG, Dell'Osso L, Pacini M, Popovic D, Rovai L, Torrens M et al (2011) Dual diagnosis and chronology of illness in treatment-seeking Italian patients dependent on heroin. J Addict Dis 30(2):123–135

Marmorstein NR (2011) Associations between subtypes of major depressive episodes and substance use disorders. Psychiatry Res 186(2–3):248–253

Martín-Santos R, Fonseca F, Domingo-Salvany A, Ginés JM, Ímaz ML, Navinés R et al (2006) Dual diagnosis in the psychiatric emergency room in Spain. Eur J Psychiatry 20:147–156
Martin-Santos R, Torrens M, Poudevida S, Langohr K, Cuyas E, Pacifici R et al (2010) 5-HTTLPR polymorphism, mood disorders and MDMA use in a 3-year follow-up study. Addict Biol 15(1): 15–22
Mendelsohn C (2012) Smoking and depression–a review. Aust Fam Physician 41(5):304–307
Morgello S, Holzer CE 3rd, Ryan E, Young C, Naseer M, Castellon SA et al (2006) Interrater reliability of the Psychiatric Research Interview for Substance and Mental Disorders in an HIV-infected cohort: experience of the National NeuroAIDS Tissue Consortium. Int J Methods Psychiatr Res 15(3):131–138
Mueller TI, Lavori PW, Keller MB, Swartz A, Warshaw M, Hasin D et al (1994) Prognostic effect of the variable course of alcoholism on the 10-year course of depression. Am J Psychiatry 151(5):701–706
Nestler EJ, Carlezon WA Jr (2006) The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59(12):1151–1159
Nunes EV, Levin FR (2004) Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA 291(15):1887–1896
Pani PP, Vacca R, Trogu E, Amato L, Davoli M (2010) Pharmacological treatment for depression during opioid agonist treatment for opioid dependence. Cochrane Database Syst Rev 9: CD008373. doi(9):CD008373.
Pettinati HM, Oslin DW, Kampman KM, Dundon WD, Xie H, Gallis TL et al (2010) A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry 167(6):668–675
Pettinati HM, O'Brien CP, Dundon WD (2013) Current status of co-occurring mood and substance use disorders: a new therapeutic target. Am J Psychiatry 170(1):23–30
Riper H, Andersson G, Hunter SB, de Wit J, Berking M, Cuijpers P (2014) Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: a meta-analysis. Addiction 109(3):394–406
Rodriguez-Llera MC, Domingo-Salvany A, Brugal MT, Silva TC, Sanchez-Niubo A, Torrens M et al (2006) Psychiatric comorbidity in young heroin users. Drug Alcohol Depend 84(1):48–55
Salo R, Flower K, Kielstein A, Leamon MH, Nordahl TE, Galloway GP (2011) Psychiatric comorbidity in methamphetamine dependence. Psychiatry Res 186(2–3):356–361
Samet S, Fenton MC, Nunes E, Greenstein E, Aharonovich E, Hasin D (2013) Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence. Addiction 108(1):115–123
Schuckit MA (2006) Comorbidity between substance use disorders and psychiatric conditions. Addiction 101(Suppl 1):76–88
Torrens M, Serrano D, Astals M, Perez-Dominguez G, Martin-Santos R (2004) Diagnosing comorbid psychiatric disorders in substance abusers: validity of the Spanish versions of the Psychiatric Research Interview for Substance and Mental Disorders and the Structured Clinical Interview for DSM-IV. Am J Psychiatry 161(7):1231–1237
Torrens M, Fonseca F, Mateu G, Farre M (2005) Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. Drug Alcohol Depend 78(1):1–22
Torrens M, Martin-Santos R, Samet S (2006) Importance of clinical diagnoses for comorbidity studies in substance use disorders. Neurotox Res 10(3–4):253–261
Torrens M, Gilchrist G, Domingo-Salvany A, psyCoBarcelona Group (2011a) Psychiatric comorbidity in illicit drug users: substance-induced versus independent disorders. Drug Alcohol Depend 113(2–3):147–156
Torrens M, Martínez-Sanvisens D, Martínez-Riera R, Bulbena A, Szerman N, Ruiz P (2011b) Dual diagnosis: focusing on depression and recommendations for treatment. Addict Disord Their Treat 10:50–59

Torrens M, Rossi PC, Martinez-Riera R, Martinez-Sanvisens D, Bulbena A (2012) Psychiatric co-morbidity and substance use disorders: treatment in parallel systems or in one integrated system? Subst Use Misuse 47(8–9):1005–1014

Vallecillo G, Mojal S, Roquer A, Martinez D, Rossi P, Fonseca F et al (2013) Risk of QTc prolongation in a cohort of opioid-dependent HIV-infected patients on methadone maintenance therapy. Clin Infect Dis 57(8):1189–1194

Valverde O, Celerier E, Baranyi M, Vanderhaeghen P, Maldonado R, Sperlagh B et al (2009) GPR3 receptor, a novel actor in the emotional-like responses. PLoS One 4(3):e4704

Valverde O, Torrens M (2012) CB1 receptor-deficient mice as a model for depression. Neuroscience 204:193–206

Vergara-Moragues E, Gonzalez-Saiz F, Lozano OM, Betanzos Espinosa P, Fernandez Calderon F, Bilbao-Acebos I et al (2012) Psychiatric comorbidity in cocaine users treated in therapeutic community: substance-induced versus independent disorders. Psychiatry Res 200(2–3): 734–741

Watkins KE, Hunter SB, Hepner KA, Paddock SM, de la Cruz E, Zhou AJ et al (2011) An effectiveness trial of group cognitive behavioral therapy for patients with persistent depressive symptoms in substance abuse treatment. Arch Gen Psychiatry 68(6):577–584

Wise RA (1989) Opiate reward: sites and substrates. Neurosci Biobehav Rev 13(2–3):129–133