Full length article

Influence of comorbid alcohol use disorders on the clinical patterns of major depressive disorder: A general population-based study

Louise Carton[a,b,*], Baptiste Pignon[c,d,e,f], Alexandre Baguet[g], Imane Benradia[h,i], Jean-Luc Roelandt[h,i], Guillaume Vaiva[j], Pierre Thomas[j], Ali Amad[j], Philippe De Timary[k], Mickaël Naassila[l], Pierre A. Geoffroy[e,m,n,o], Benjamin Rolland[p,q]

[a] Univ Lille, Inserm, CHU de Lille, UMR_S1171 and Service de Pharmacologie Médicale, F-59000 Lille, France
[b] CHU Lille Service d'Addictologie et de Psychiatrie, France
[c] AP-HP, DHU PePSY, Hôpitaux Universitaires Henri-Mondor, Pôle de Psychiatrie, Créteil, 94000, France
[d] INSERM, U955, Team 15, Créteil, 94000, France
[e] Fondation FondaMental, Créteil, 94000, France
[f] UPEC, Université Paris-Est, Faculté de Médecine, Créteil, 94000, France
[g] Service d'Addictologie, CHU de Rouen, Rouen, France, INSERM, U1073, Rouen, France, Institut de Recherche et d'Innovation en Biomedecine, Université de Normandie, Rouen, France
[h] Centre Collaborateur de l'Organisation Mondiale de la Santé—CCOMS (Lille, France), EPSM Lille Métropole, France
[i] Inserm, UMR 1123-ECEVE—Université Paris Diderot, France
[j] Univ. Lille, CNRS UMR 9193-PsyCHIC-SCALab & CHU Lille, Department of Psychiatry, F-59000 Lille, France
[k] Service Psychiatrie Adulte et Institut de Neurosciences, Clinique universitaire Saint Luc, Université catholique de Louvain, Avenue Hippocrate 10, B1200 Bruxelles, Belgium
[l] Univ Picardie Jules Verne, Centre Universitaire de Recherche en Santé, INSERM U1247 Unit, Research Group on Alcohol and Pharmacodependences (GRAP), Amiens, France
[m] Inserm, U1144, Paris F-75006, France
[n] Université Paris Diderot, Sorbonne Paris Cité, UMR-S 1144, Paris F-75013, France
[o] AP-HP, GH Saint-Louis—Lariboisière—F. Widal, Pôle de Psychiatrie et de Médecine Addictologique, 75475 Paris Cedex 10, France
[p] Service Universitaire d'Addictologie de Lyon (SUAL), Pôle MOPHA, CH Le Vinatier, 69500 Bron, France
[q] Univ Lyon; UCBL; CRNL; Inserm U1028; CNRS UMR5292, 69678 Bron, France

ARTICLE INFO

ABSTRACT

Background: To compare the symptom patterns of major depressive disorder (MDD) among subjects with MDD and 1) no alcohol use disorder (AUD), 2) alcohol abuse and 3) alcohol dependence, respectively.

Methods: In a general population survey of 38,694 French individuals, MDD and AUDs were assessed using the Mini International Neuropsychiatric Interview 5.0.0 (MINI). A total of 4339 subjects (11.2%) in the sample met the criteria for MDD. Among them, 413 (9.5%) AUD subjects were identified: 138 (3.2%) for alcohol abuse and 275 (6.3%) for alcohol dependence. The associations of each of the ten MDD criteria of the MINI and psychiatric clinical features were compared among the three groups. The relative profiles of 'MDD + AUD' vs. 'MDD alone' were determined using a multivariable stepwise regression model.

Results: With the noAUD group as the reference, sadness (OR = 0.46; 95%CI, 0.29–0.74) and anhedonia (OR = 1.66; 95%CI, 1.06–2.73) were only associated with alcohol abuse. Sleep disorders (OR = 2.07; 95%CI, 1.51–2.88), feelings of guilt (OR = 1.41; 95%CI, 1.05–1.90), diminished concentration/indecisiveness (OR = 1.52; 95%CI, 1.12–2.07) and thoughts of death (OR = 1.95; 95%CI 1.49–2.55) were only associated with alcohol dependence. Weight or appetite variations were both associated with alcohol abuse (OR = 1.7; 95%CI, 1.15–2.53) and dependence (OR = 1.41; 95%CI, 1.06–1.88). Bipolar disorder and PTSD were only associated with alcohol dependence. Psychotic features, previous suicide attempts, and panic disorder were more frequent in the MDD-AUD group.

Conclusion: MDD-AUD subjects displayed a more severe profile with specific symptomatology and comorbidity profiles compared to MDD-only subjects.

* Corresponding author at: Département de Pharmacologie Médicale, Université de Lille, Faculté de Médecine, Pôle Recherche, 1 Place de Verdun, 59045 Lille Cedex, France.
  E-mail address: louise.carton@univ-lille2.fr (L. Carton).

1. Introduction

Dual diagnoses are specific clinical entities that do not merely consist of the simple adding of characteristics of each underlying disorder but also possess specific vulnerability factors, specific outcomes, and specific clinical features (Brady et al., 2007; Morojele et al., 2012). The association between major depressive disorder (MDD) and alcohol use disorders (AUDs), *i.e.*, alcohol dependence or abuse, is one of the most common types of dual diagnoses. Bidirectional chronological relationships have been found in the co-occurrence of MDD and AUDs (Gilman and Abraham, 2001; Pacek et al., 2013). A stronger association has been reported between alcohol dependence and MDD compared to the association between alcohol abuse and MDD (Cranford et al., 2011; Dawson et al., 2005; Grant and Harford, 1995; Pacek et al., 2013). Compared to MDD and AUDs alone, comorbid AUDs and MDD also display specifically worse outcomes, including a shorter time to re-hospitalization (Lin et al., 2007), an elevated risk of premature death due to suicide or other unnatural death (Yoon et al., 2011), or lower global functioning and dissatisfaction (Brière et al., 2014).

Moreover, the MDD criteria encompass a group of disorders that are heterogeneous with respect to their supposed pathophysiology and clinical expression (Hasler et al., 2004). Indeed, different forms of MDD have been associated with distinct biological, psychological, and behavioral correlates and potentially distinct etiologies (Fountoulakis et al., 2004; Gottesman and Gould, 2003; Leventhal et al., 2008). It is therefore important to analyze the specificities of the clinical profile of MDD associated with AUDs compared to MDD without AUDs based on individual key MDD symptoms. This would allow the isolation of phenotypic markers, possibly representing more direct expressions of underlying genes, neurophysiology, and psychosocial processes, thus identifying endophenotypes of this heterogeneous MDD entity (Gottesman and Gould, 2003; Hasler et al., 2004; Leventhal et al., 2011).

To our knowledge, few previous studies have focused on the difference in the distribution of the diagnostic criteria for MDD between expressions with and without AUDs or even SUDs (Blanco et al., 2012; Cornelius et al., 1995; Davis et al., 2006). In those studies, individuals with MDD and SUDs presented with a larger number of DSM-IV MDD criteria than those with MDD alone. Moreover, they displayed more symptoms, such as sleep disorders, feelings of worthlessness, loss of interest, thoughts of death, and suicide attempts, but were less likely to report sadness (Blanco et al., 2012). According to the ICDS-30 criteria (30-item Inventory of Depressive Symptomatology-Clinician Rated), MDD-SUDs subjects presented more irritable moods, mood variation, negative outlook of oneself, sympathetic arousal and gastrointestinal symptoms (Davis et al., 2006). Furthermore, depressive symptoms, such as suicidality and low self-esteem, were more pronounced among MDD subjects with alcohol dependence (Cornelius et al., 1995). Overall, previous studies did not distinguish between alcohol dependence and abuse. Moreover, they were not based on multivariable modeling, especially for controlling other clinical dimensions of MDD (*e.g.*, previous suicide attempts or bipolar or psychotic characteristics) or other comorbid associations (*e.g.*, other SUDs or comorbid anxiety disorder).

In the present study, we explored the distribution of the clinical criteria for MDD among MDD subjects with and without AUDs using a French general population survey. We also explored other clinical features of MDD and other comorbidities, and we built a step-by-step multivariable model that explored the global clinical profile of the MDD-AUD association. The study is reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Von Elm et al., 2007) (see Supplemental material STROBE statement).

We hypothesized that MDD-AUDs will present a more severe profile than MDD without AUDs with a gradient of severity where the MDD-alcohol abuse group experiences greater severity than MDD without AUD and less severity than the MDD-alcohol dependence group.

2. Materials and methods

2.1. Sample

The Mental Health in the General Population (MHGP) survey was conducted by trained nurses for 38,694 subjects in France between 1999 and 2003. The participants were selected at 47 sites (900 subjects per site) using a quota sampling method (Lunsford and Lunsford, 1995) based on age, gender, educational level, and occupational category according to census figures from 1999 provided by the French National Institute for Statistics and Economic Studies. Subjects were included in the study if they met the following criteria: 1) provides informed consent to participate in the survey, 2) is a French speaker, 3) is at least 18 years of age and 4) is neither institutionalized nor homeless. Additional methodological details can be found elsewhere (Amad et al., 2013; Caria et al., 2010; Grolleau et al., 2008; Leray et al., 2011; Pignon et al., 2017a,b; Rolland et al., 2017; Tebeka et al., 2018).

2.2. Data collection and group constitution

The following socio-demographic characteristics were collected: age, gender, education level, income level, marital status and native variable. All participants were screened for Axis-I mental disorders, including AUDs and MDD, using the Mini International Neuropsychiatric Interview (MINI, French version, 5.0.0) (Sheehan et al., 1997).

The ten categorical criteria used for screening MDD in the MINI were individually collected: 1) sadness, 2) anhedonia, 3) fatigue or loss of energy, 4) weight or appetite variations, 5) sleep disorders, 6) psychomotor retardation or agitation, 7) feelings of worthlessness, 8) feelings of guilt, 9) diminished concentration/indecisiveness and 10) thoughts of death.

Several other features of MDD were also screened using the MINI: 1) bipolar disorder (*i.e.*, previous history of mania), 2) psychotic characteristics (estimated using the screening of lifetime psychotic symptoms in the MINI) and 3) previous suicide attempts. Comorbid SUDs other than alcohol were also screened. Finally, anxiety comorbidities were also screened: 1) panic disorder with or without agoraphobia, 2) social phobia, 3) generalized anxiety disorder (GAD) and 4) post-traumatic stress disorder (PTSD).

Only the subsample of subjects meeting the criteria for MDD was used for this study. The MDD subjects were divided into three groups: 1) subjects with comorbid alcohol dependence, 2) subjects with comorbid alcohol abuse and 3) subjects with no comorbid AUD ("noAUD" group). In some subsequent analyses, the combined abuse and dependence groups were pooled into an 'AUD' group.

Of the 38,694 survey participants, 4339 subjects (11.2%) met the criteria for MDD. In the MDD population, 413 AUD subjects (9.5%) were identified, including 138 subjects (3.2%) with alcohol abuse and 275 subjects (6.3%) with alcohol dependence. From the sample, 261 subjects (6.0%) also met the criteria for SUDs, including 100 subjects (2.3%) with both SUDs and AUDs.

2.3. Ethics procedures

The MHGP study protocol was submitted to and approved by the *Commission Nationale Informatique et Liberté* (CNIL) and the *Comité consultatif sur le traitement de l'information en matière de recherche* (CCTIRS; #98.126).

2.4. Statistical analyses

For each of the ten categorical clinical items of MDD, bivariate comparisons were conducted on the different sociodemographic features using chi-square tests. Based on a previous study (Blanco et al., 2012), a series of multivariable logistical binomial regression analyses

were conducted, with each of the categorical clinical features of MDD being the dependent variable and the predefined groups being the independent variable. Sociodemographic variables that were found to be associated with a significance level of α = 0.2 with at least one MDD symptom in the bivariate analyses were included in all binomial logistic regressions as adjustment variables. Because a comorbid SUD might substantially alter the result analyses, comorbid SUDs were included as an *a priori* adjustment factor, and sensitivity analyses were conducted using the sample without subjects with a comorbid SUD. Moreover, because bipolar disorder has a specific profile regarding both the clinical criteria of depression and the addictive and anxiety comorbidities (Baethge et al., 2005; Furukawa et al., 2000; Geoffroy et al., 2017), sensitivity analyses were conducted using the sample without subjects with bipolar disorder. For all these analyses, we also indicate of the variables that met statistical significance after applying a Bonferroni correction for multiple testing.

Furthermore, a multivariable backward step-by-step regression model was built, with the AUD group variable being the dependent variable. The independent variables initially included in the model consisted of 1) the ten MDD clinical features, 2) the different sociodemographic variables, 3) bipolar disorder, 4) psychotic characteristics, 5) comorbid SUD and 6) each of the different anxiety disorders. At each step, the least significant variable was removed to compute the next step. The best fitting model with all significant independent variables (at a level of α = 0.05) was retained.

All statistical analyses were performed using R software (http://www.R-project.org/).

3. Results

3.1. Descriptive statistics

The detailed sociodemographic characteristics of the MDD sample can be found in Table 1.

In total, 208 MDD subjects (4.8%) met the criteria for bipolar disorder, while 1578 subjects (36.4%) reported lifetime psychotic symptoms, and 756 individuals (17.4%) reported previous suicide attempts.

Finally, 864 subjects (19.9%) met the criteria for panic disorder, while 522 subjects (12.0%) met the criteria for social phobia, 1278 subjects (29.5%), for GAD, and 92 subjects, (2.1%), for PTSD.

3.2. Results of the analyses on MDD diagnostic criteria

All sociodemographic variables were significantly associated with at least one of the ten clinical criteria for MDD, and they were thus all included in the multivariable logistical binomial regression analyses. The results of the analyses comparing the frequency of the ten clinical criteria for MDD according to the AUD status can be found in Table 2 (sample includes subjects with comorbid SUDs) and Table 3 (sample excludes subjects with comorbid SUDs). Each of the categorical clinical features of MDD was the dependent variable and the predefined groups the independent variables. Analyses were adjusted on marital status, level of income, level of education and native variable.

In the sample that included subjects with comorbid SUDs (Table 2) and with the group 'noAUD' as the reference, sadness was negatively associated with alcohol abuse (OR = 0.46; 95%CI, 0.29–0.74) but not with alcohol dependence. Anhedonia was positively associated with alcohol abuse only (OR = 1.66; 95%CI, 1.06–2.73), while weight or appetite variations were positively associated with alcohol abuse (OR = 1.70; 95%CI, 1.15–2.53) and alcohol dependence (OR = 1.41; 95%CI, 1.06–1.88, respectively). Furthermore, several clinical features of MDD were positively associated only with alcohol dependence: sleep disorders (OR = 2.07; 95%CI, 1.51–2.88), feelings of guilt (OR = 1.41; 95%CI, 1.05–1.09), diminished concentration/indecisiveness (OR = 1.52; 95%CI, 1.12–2.07) and thoughts of death (OR = 1.95; 95%CI, 1.49–2.55). After the Bonferroni correction, all associations remained significant, except the associations between anhedonia and alcohol abuse, between weight or appetite variations and both AUDs, and between feelings of guilt, diminished concentration/indecisiveness and alcohol dependence.

In the sample that excluded subjects with comorbid SUDs (Table 3), anhedonia was no longer associated with alcohol abuse, and weight and appetite variations were no longer associated with alcohol dependence. Conversely, feelings of worthlessness were positively associated with

Table 1
Sociodemographic characteristics of subjects with and without AUDs

	MDD[a] without AUDs[b] (N = 3926)	MDD with AUDs (N = 413)		p-values[*]
		MDD with alcohol abuse (N = 138)	MDD with alcohol dependence (N = 275)	
Mean age (standard deviation)	43.9 (18.9)	36.7 (13.2)	36.8 (13.1)	< 0.001
Gender (%)				< 0.001
Male	33.9	71.0	72.4	
Female	66.1	29.0	27.6	
Education level (%)				< 0.001
No education-elementary level	27.8	20.3	21.8	
College level	52.3	64.5	61.1	
University level	19.8	15.2	17.1	
Income level[c] (%)				0.007
Low	52.3	56.7	62.1	
Medium	34.1	29.9	29.6	
High	13.6	13.4	8.3	
Marital status (%)				< 0.001
Married	43.7	32.1	26.1	
Never married	32.1	46.7	47.8	
Separated	12.0	19.0	21.7	
Widowed	12.2	2.2	4.4	
Native variable				0.52
French-Native[c]	92.9	97.8	91.6	
1GM[d]	7.1	2.2	8.4	

[a] MDD: Major Depressive Disorder.
[b] AUDs: Alcohol Use Disorders.
[c] Native: born in metropolitan France.
[d] 1GM: First-generation migrant, *i.e.* born outside metropolitan France.
[*] Comparisons between MDD with AUD and without AUD using the *t*-test and chi-squared test.

Table 2

Comparison of rates of MDD symptoms, clinical features and anxiety comorbidities according to the AUD status

	noAUD Group		Alcohol Abuse Group		Alcohol Dependence Group	
	%	OR [95% CI]	%	OR [95% CI]	%	OR [95% CI]
MDD symptoms						
Sadness	91.0		81.2	0.46 [0.29–0.74]***,+	89.1	0.93 [0.61–1.46]
Anhedonia	75.2	–	82.6	1.66 [1.06–2.73]*	80.7	1.27 [0.92–1.78]
Fatigue or loss of energy	86.7	–	87.0	1.16 [0.71–2.00]	83.6	0.96 [0.67–1.40]
Weight or appetite variations	59.4	–	72.5	1.70 [1.15–2.53]**	68.7	1.41 [1.06–1.88]*
Sleep disorders	67.2	–	69.6	1.18 [0.81–1.75]	78.5	2.07 [1.51–2.88]***,+
Psychomotor retardation or agitation	53.8	–	55.8	1.09 [0.77–1.56]	61.1	1.29 [0.99–1.70]
Feelings of worthlessness	61.9	–	60.1	0.88 [0.62–1.27]	66.7	1.20 [0.91–1.60]
Feelings of guilt	59.4	–	68.1	1.23 [0.85–1.82]	73.0	1.41 [1.05–1.90]*
Diminished concentration/indecisiveness	66.0	–	67.4	1.01 [0.70–1.49]	76.4	1.52 [1.12–2.07]**
Thoughts of death	37.6	–	42.0	1.19 [0.83–1.71]	53.8	1.95 [1.49–2.55]***,+
Associated clinical features						
Bipolar disorder	4.0		8.7	1.49 [0.75–2.71]	14.6	2.18 [1.42–3.30]***,+
Psychotic characteristic	41.5	–	66.7	2.31 [1.59–3.39]***,+	65.1	1.90 [1.44–2.53]***,+
Previous suicide attempts	20.1	–	36.1	2.24 [1.45–3.41]***,+	44.5	2.94 [2.17–3.98]***,+
Anxiety comorbidities						
Panic disorder	18.9	–	26.8	1.63 [1.08–2.43]*	31.6	1.91 [1.41–2.56]***,+
Social phobia	11.6	–	13.8	1.20 [0.70–1.95]	17.1	1.31 [0.90–1.88]
GAD	29.4	–	34.8	1.29 [0.89–1.86]	27.3	0.91 [0.68–1.22]
PTSD	1.7	–	4.4	2.44 [0.91–5.50]	6.6	3.19 [1.70–5.72]***,+

Abbreviations: MDD: Major Depressive Disorder; AUDs: Alcohol Use Disorders; GAD: Generalized anxiety disorder; PTSD: Posttraumatic stress disorder; OR: Odds-Ratio; CI 95%: 95% Confidence Interval.

OR and 95% CI result from multivariable logistical binomial regression with each of the categorical clinical features of MDD being the dependent variables and alcohol abuse and dependence being the independent variables. AUD status reference category was no AUD. Analyses were adjusted on marital status, level of income, level of education and native variable.

* p-value < 0.05.

** p-value < 0.005.

*** p-value < 0.0005.

+ Significant after Bonferroni correction (*i.e.* at a level α = 0.0029).

Table 3

Sensitivity analyses: Comparison of rates of MDD symptoms, clinical features and anxiety comorbidities according to AUD status in the sample without SUDs

	NoAUD Group		Alcohol Abuse Group		Alcohol Dependence Group	
	%	OR [95% CI]	%	OR [95% CI]	%	OR [95% CI]
MDD symptoms						
Sadness	91.0		81.0	0.43 [0.27–0.72]***,+	87.3	0.77 [0.49–1.26]
Anhedonia	75.2	–	80.1	1.46 [0.91–2.44]	81.2	1.30 [0.90–1.94]
Fatigue or loss of energy	86.7	–	87.0	1.20 [0.70–2.18]	84.6	1.10 [0.73–1.73]
Weight or appetite variations	59.2	–	72.4	1.67 [1.11–2.58]*	66.5	1.33 [0.97–1.85]
Sleep disorders	67.5	–	72.4	1.34 [0.88–2.08]	77.6	1.87 [1.31–2.74]***,+
Psychomotor retardation or agitation	53.7	–	56.0	1.12 [0.76–1.65]	57.9	1.17 [0.86–1.59]
Feelings of worthlessness	65.8	–	67.2	1.06 [0.71–1.61]	74.1	1.40 [1.01–1.99]*
Feelings of guilt	58.8	–	65.5	1.19 [0.80–1.81]	71.4	1.44 [1.04–2.01]*
Diminished concentration/indecisiveness	65.8	–	67.2	1.06 [0.71–1.61]	74.1	1.40 [1.01–1.99]*
Thoughts of death	37.7	–	39.7	1.10 [0.74–1.63]	52.8	1.92 [1.42–2.62]***,+
Clinical features						
Bipolar disorder	3.5		8.6	1.97 [0.93–3.76]	13.2	2.98 [1.79–4.79]***,+
Psychotic characteristic	40.3	–	64.7	2.45 [1.65–3.69]***,+	60.4	1.97 [1.44–2.69]***,+
Previous suicide attempts	19.5	–	33.7	2.20 [1.37–3.49]***,+	43.0	3.26 [2.30–4.59]***,+
Anxiety comorbidities						
Panic disorder	18.5	–	24.1	1.60 [1.01–2.47]*	27.4	1.87 [1.41–2.62]***,+
Social phobia	11.5	–	12.9	1.20 [0.66–2.04]	11.7	0.98 [0.59–1.56]
GAD	29.5	–	37.9	1.43 [0.96–2.10]	28.9	0.96 [0.69–1.33]
PTSD	1.7	–	4.3	2.69 [0.91–6.44]	4.6	2.74 [1.22–5.55]***,+

Abbreviations;: MDD: Major depressive disorder; AUDs: Alcohol use disorders; OR: Odds-ratio; GAD: Generalized anxiety disorder; PTSD: Posttraumatic stress disorder; SUDs: Substance Use Disorders; OR: Odds-ratio; CI 95%: 95% confidence interval.

OR and 95% CI result from multivariable logistical binomial regression with each of the categorical clinical features of MDD being the dependent variables and alcohol abuse and dependence being the independent variables. AUD status reference category was no AUD. Analyses were adjusted on marital status, level of income, level of education and native variable.

**p-value < 0.005.

* p-value < 0.05.

*** p-value < 0.0005.

+ Significant after Bonferroni correction (*i.e.* at a level α = 0.0029).

Table 4
Sensitivity analyses: Comparison of rates of MDD symptoms, clinical features and anxiety comorbidities according to AUD status in the sample without BD

	NoAUD Group		Alcohol Abuse Group		Alcohol Dependence Group	
	%	OR [95% CI]	%	OR [95% CI]	%	OR [95% CI]
MDD symptoms						
Sadness	90.8		81.8	0.50 [0.31–0.83]**	88.1	0.85 [0.55–1.35]
Anhedonia	75.0	–	82.5	1.73 [1.08–2.91]*	80.0	1.31 [0.93–1.88]
Fatigue or loss of energy	86.6	–	86.5	1.11 [0.67–1.95]	83.8	0.99 [0.67–1.48]
Weight or appetite variations	58.8	–	73.0	1.80 [1.20–2.75]**	65.5	1.29 [0.96–1.74]
Sleep disorders	66.9	–	68.3	1.12 [0.76–1.68]	76.9	1.94 [1.39–2.75]***,+
Psychomotor retardation or agitation	52.9	–	52.4	1.00 [0.69–1.46]	58.7	1.29 [0.97–1.72]
Feelings of worthlessness	61.2	–	61.1	0.91 [0.63–1.34]	69.0	1.36 [1.01–1.86]*
Feelings of guilt	58.8	–	67.5	1.22 [0.82–1.83]	71.8	1.36 [0.99–1.87]
Diminished concentration/indecisiveness	65.5	–	65.0	0.94 [0.64–1.39]	76.2	1.56 [1.14–2.18]**
Thoughts of death	36.7	–	41.3	1.24 [0.85–1.81]	53.2	2.13 [1.59–2.84]***,+
Clinical features						
Psychotic characteristic	40.0	–	65.9	2.45 [1.66–3.66]***,+	63.4	2.00 [1.48–2.70]***,+
Previous suicide attempts	18.8	–	35.1	2.42 [1.53–3.78]**	39.5	2.74 [1.96–3.82]***,+
Anxiety comorbidities						
Panic disorder	17.5	–	25.4	1.71 [1.32–2.55]*	28.1	1.84 [1.10–2.60]***,+
Social phobia	11.0	–	11.9	1.11 [0.61–1.90]	15.8	1.39 [0.91–2.06]
GAD	29.6	–	35.7	1.34 [0.91–1.96]	27.7	0.92 [0.67–1.25]
PTSD	1.5	–	4.8	3.13 [1.15–7.21]*	6.0	3.40 [1.68–6.51]***,+

Abbreviations;: MDD: Major depressive disorder; AUDs: Alcohol use disorders; OR: Odds-ratio; GAD: Generalized anxiety disorder; PTSD: Posttraumatic stress disorder; OR: Odds-ratio; CI 95%: 95% confidence interval.
OR and 95% CI result from multivariable logistical binomial regression with each of the categorical clinical features of MDD being the dependent variables and alcohol abuse and dependence being the independent variables. AUD status reference category was no AUD. Analyses were adjusted on marital status, level of income, level of education and native variable.
  * p-value < 0.05.
 ** p-value < 0.005.
*** p-value < 0.0005.
  + Significant after Bonferroni correction (*i.e.* at a level α = 0.0031).

alcohol dependence (OR = 1.40; 95%CI, 1.01–1.99). After the Bonferroni correction, all associations remained significant, except the associations between weight and appetite variations and alcohol abuse and between feelings of worthlessness, feelings of guilt, diminished concentration/indecisiveness and alcohol dependence.

In the sample that excluded bipolar disorder (Table 4), before the Bonferroni correction, all associations remained significant (in comparison to Table 2), except for weight and appetite variations, feeling of guilt and alcohol dependence. However, the association between feelings and worthlessness and alcohol dependence became significant (OR = 1.36 95%CI, 1.01–1.86). After the Bonferroni correction, in this sample, sadness was no longer associated with alcohol abuse.

3.3. Results of the analyses on other characteristics of the MDD population

Bipolar disorder was associated only with alcohol dependence (OR = 2.18; 95%CI, 1.42–3.30). Psychotic characteristics and previous suicide attempts were associated with both alcohol abuse (respectively, OR = 2.31 95%CI, 1.59–3.39 and OR = 2.24; 95%CI, 1.45–3.41) and alcohol dependence (OR = 1.90; 95%CI, 1.44–2.53 and OR = 2.94; 95%CI, 2.17–3.98) (Table 2). The results were similar in the sample without SUDs (Table 3). After the Bonferroni correction, all associations remained significant in the samples with and without SUD (Table 3).

Panic disorder was associated with alcohol abuse (OR = 1.63; 95%CI, 1.08–2.43) and alcohol dependence (OR = 1.91; 95%CI, 1.41–2.56). PTSD was associated only with alcohol dependence (OR = 3.19; 95%CI, 1.70–5.72) but not alcohol abuse (Table 2). The results were similar in the sample without SUDs (Table 3). After the Bonferroni correction, all associations remained significant, except for the association between panic disorder and alcohol abuse.

In the sample that excluded bipolar disorder (Table 4), before the Bonferroni correction, all associations remained significant (in comparison to Table 2). The association between PTSD, and alcohol abuse became significant (OR = 3.13 95%CI, 1.15–7.21). After the Bonferroni

correction, all associations remained significant except for previous suicide attempts, panic disorders, PTSD, and alcohol abuse.

3.4. Results of the backward step-by-step regression modeling

In total, 24 variables (*i.e.*, six sociodemographic variables, the SUD status, the ten MDD criteria, the three associated clinical features of MDD, and the three anxiety disorders variables) were included as explanatory variables in two stepwise descending analyses (one for alcohol abuse, one for alcohol dependence). This model progressively eliminates the explanatory variables not found statistically associated with the dependent variables. The last step of each analysis is presented in Table 5. Only the variables significantly associated with alcohol abuse or alcohol dependence are exhibited, and the reported associations are estimated taking into account all other variables included in the model.

4. Discussion

The main objective of the study was to compare the MDD symptom patterns and psychiatric comorbidities of subjects with a current MDD according to their AUD status using a cross-sectional survey of a French national community-based sample.

First, our overall data seem consistent with previous findings of the epidemiology of MDD, as we found a prevalence rate of 11.2% for MDD according to the MINI. If a previous study found a twelve-month MDD prevalence of 5.3% in the adult US population (Hasin et al., 2005), in the French population, however, the prevalence of last-month and twelve-month MDD has been found to be 12% and 7.8%, respectively (Lamboy et al., 2007; Le Pape and Lecomte, 1999). The differences between French and US prevalence can be explained by the different methodologies and questionnaires used. Moreover, among US patients with MDD in the prior 12 months, 14% met the criteria for AUD, and nearly 5% met the criteria for SUDs (Hasin et al., 2005), which is

Table 5

Final models of stepwise descending multinomial logistical regression analyses for the 'alcohol abuse' and 'alcohol dependence' variables in MDD sample

	p-value	OR [95% CI]
Alcohol abuse		
Age-band[a]:		
18–29 years	0.001	6.31 [2.21–17.97]
30–44 years	0.002	5.16 [1.80–14.80]
45–59 years	0.001	5.81 [2.00–16.84]
Female gender	< 0.001	0.18 [0.12–0.29]
First-generation migrant	0.045	0.30 [0.09–0.97]
Sadness	< 0.001	0.41 [0.25–0.67]
Psychotic symptoms	0.002	1.98 [1.29–3.04]
Previous suicide attempts	0.002	1.94 [1.27–2.97]
Panic disorders	0.024	1.69 [1.07–2.65]
Alcohol dependence		
Age-band[a]:		
18–29 years	0.008	2.60 [1.28–5.26]
30–44 years	0.001	2.97 [1.53–5.77]
45–59 years	0.003	2.75 [1.41–5.36]
Female gender	< 0.001	0.23 [0.17–0.32]
Separated marital status[c]	< 0.001	2.42 [1.44–3.01]
Sleep disorders	< 0.001	1.97 [1.38–2.81]
Diminished concentration/indecisiveness	0.031	1.44 [1.03–1.99]
Psychotic symptoms	0.017	1.45 [1.07–1.97]
Previous suicide attempts	< 0.001	2.57 [1.90–3.48]
PTSD	0.011	2.34 [1.22–4.50]
SUDs[b]:		
Substance dependence	< 0.001	4.09 [1.98–8.45]
Substance abuse	< 0.001	4.64 [3.02–7.13]

Abbreviations;: MDD: Major depressive disorder; AUD: Alcohol use disorders; OR: Odds-ratio; 95% CI: 95% Confidence Interval; PTSD: Posttraumatic Stress Disorder.

OR and CI 95% result from stepwise analyses looking for factors specifically associated with alcohol abuse and dependence status.

The AUD group variable is the dependent variable. The independent variables initially included in the model consisted of 1) the ten MDD features, 2) the different sociodemographic variables, 3) bipolar disorder, 4) psychotic characteristics, 5) comorbid SUD and 6) each of the different anxiety disorders. The reported associations are therefore estimated taking into account all those variables.

[a] Reference age-band category was 60 +.

[b] Reference category was no SUD.

[c] Reference marital status category was 'living with a partner'.

relatively consistent with our results (*i.e.*, 9.5% of the MDD subjects met the criteria for AUDs, while 6% met the criteria for SUDs).

The results of the comparisons in the expression of the different symptom patterns of MDD according to the alcohol status, based on the multivariable binomial regression analyses, raise several reflections. After the Bonferroni correction, and with the 'noAUD' group as the reference, sadness was negatively associated with alcohol abuse but not alcohol dependence. A similar negative association was observed in the sample without SUDs. By comparison, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found that MDD subjects with SUDs presented less depressed moods than MDD without SUDs. However, they did not distinguish between the different types of substances used and did not assess the diagnoses of abuse or dependence (Blanco et al., 2012). The reduced level of sadness among subjects with alcohol abuse could reflect the direct dysphoric action of alcohol in these subjects. In subjects with alcohol dependence, the depressive effects of alcohol progressively prevail over the dysphoric effects in the long term, (Fergusson et al., 2009) which could explain why MDD subjects with alcohol dependence have no reduced sadness compared to MDD subjects with noAUD.

By contrast, other MDD symptoms were significantly increased in subjects with alcohol dependence, but not those with alcohol abuse. This was the case for sleep disorders, which is consistent the results of a previous study, which found that more than half of the subjects with alcohol dependence reported sleep disorders (Brower, 2015). Moreover,

among MDD subjects with alcohol dependence, the level of alcohol use predicts the severity of insomnia (Zhabenko et al., 2013). Self-medication of insomnia with alcohol may be frequent among subjects with alcohol dependence, but there is a general scientific consensus that both acute and chronic alcohol use disrupt sleep patterns (Brower et al., 2001). However, the literature is relatively unclear on this point, and other previous studies did not find any difference in the occurrence of sleep disorders between MDD subjects with and without AUDs or SUDs (Cornelius et al., 1995; Davis et al., 2006).

Furthermore, suicidal thoughts were another MDD symptom found specifically associated with alcohol dependence in our study. This is also consistent with previous studies reporting higher suicidal ideation and suicide attempts in MDD individuals with alcohol dependence (Cornelius et al., 1996, 1995; Sher et al., 2008, 2005). The mechanisms underlying this relationship are debated. A previous study hypothesized that the higher rate of ideal thoughts and suicide attempts in MDD subjects with alcohol dependence could be explain by a higher level of predisposing (aggression/impulsivity, severe alcoholism, negative affect and hopelessness) and precipitating factors (stressful life events, particularly interpersonal difficulties) (Conner and Duberstein, 2004; Sher et al., 2005).

In our study, other clinical features were compared in MDD subjects depending on the alcohol status. Associated psychotic characteristics were found to be more frequent in both the 'alcohol abuse' and 'alcohol dependence' groups compared to the 'noAUD' group. Sensitivity analyses did not provide substantially different results. Previous studies also found a strong association between AUDs and psychotic disorders, with over one-third of patients with schizophrenia presenting criteria for an AUD (Green and Brown, 2006; Regier et al., 1990).

Concerning anxiety comorbidities, panic disorder and PTSD were associated only with alcohol dependence. No significant association was found between social phobia or GAD and AUDs. Overall, previous studies also found that in the general population, AUDs were significantly associated with anxiety disorder (Bailey et al., 2012; Fuehrlein et al., 2016; Suttajit et al., 2012). However, a recent study based on the DSM-5 criteria did not find any association between PTSD and AUDs after controlling for socio-demographic features and other psychiatric disorders (Smith et al., 2016). Moreover, studies based on the NESARC found associations between 12-month AUDs and phobia but not with panic disorder, agoraphobia, GAD or PTSD. However, lifetime moderate and severe AUDs were associated with panic disorder and severe AUDs with PTSD, which is more consistent with our results (Grant et al., 2015). MDD subjects with AUDs may have a trauma history which makes them vulnerable to depression, or alternatively, may have a milder depression and a subsequent trauma event. Alcohol could have then been used to manage these chronic and comorbid symptoms (Bailey et al., 2012). The reasons for which panic disorder, but not GAD nor social phobia, was associated with alcohol dependence, remain unclear. It could reflect the fact that alcohol is used as self-medication for preventing panic attacks, and/or that alcohol dependence increases the likelihood of developing or maintaining panic disorder.

In our findings, experiencing bipolar disorder was specifically associated with alcohol dependence. This is consistent with a precedent study that found an association between AUDs and bipolar disorder among MDD subjects (Yoon et al., 2015). We also performed a sensitivity analysis that excluded the diagnosis of bipolar disorder, considering that MDD subjects with bipolar disorder could exhibit specific features of depression. After the Bonferroni correction, in the sample without bipolar disorder, sadness was no longer negatively associated with alcohol abuse, while previous suicide attempts were no longer positively associated with alcohol abuse.

Last, the results of the multivariable modeling of the clinical profile between MDD subjects without AUDs and alcohol abuse and dependence groups found that younger age and male gender were associated with both AUDs. These results are consistent with previous studies reporting an association between MDD-AUDs or MDD-SUDs and younger

age (Davis et al., 2006, 2005; Sher et al., 2008) or male gender (Davis et al., 2006, 2005; Rodgers et al., 2014; Schuch et al., 2014). As we discussed before, sadness was strongly negatively associated with alcohol abuse, whereas separated marital status, sleep disorders and SUDs were strongly positively associated with alcohol dependence.

Overall, these results have several implications. In line with a dual-diagnosis approach, we found that MDD-AUD subjects, especially those with alcohol dependence, exhibit a specific clinical profile and presented much more frequent additional comorbidities, suggesting that they constitute a specific subpopulation with increased severity markers among MDD subjects.

The study has several limitations that should be addressed. First, the data collected were relatively old because the MHGP study ended in 2003. However, this limitation allowed direct comparison with the American NESARC cohort, which was more or less conducted in the same period. Moreover, it is unlikely that the specific clinical patterns of MDD subjects with AUDs may have specifically changed since 2003. Another possible limitation of the study was that the sampling was non-probabilistic and was performed using a quota within regions. However, several methodological precautions were taken in the MHGP survey to mitigate this issue, including the adjustment of each site's subsample based on local data from the 1999 French Census (Caria et al., 2010; Cohidon, 2007). Moreover, numerous similar large-sample studies exploring mental health issues, including the NESARC, have also been based on a quota-sampling strategy, which yields the same sociodemographic characteristics as those of the general population. Moreover, the study has an observational cross-sectional design that does not permit causal inferences (Bradford-Hill, 1965). In addition, our multivariable model only included the most frequent psychiatric comorbidities, *i.e.*, bipolar disorder, anxiety disorders, and other SUDs. However, some other comorbidities, like personality disorders, were not included, which can affect our main findings. Another possible limitation is that some participants may have incorrectly responded to the MINI interview concerning AUDs, which is relatively common due to the social desirability bias (Davis et al., 2010). Finally, the sample was limited to subjects who met the criteria for a full MDD. Future studies could more specifically compare the prevalence and clinical characteristics of individuals according to dimensional outcomes and subclinical depression.

5. Conclusion

In a French general population sample, MDD subjects with AUDs showed a more severe clinical profile with a wider array of symptoms and more comorbidities compared to MDD subjects without AUDs. This is in line with the "dual diagnosis" approach, according to which comorbid psychiatric and addictive disorders constitute specific entities with specific clinical features and increased severity factors. Moreover, our findings were the first to differentiate between alcohol abuse and dependence, thereby showing that alcohol abuse also exhibited some distinctive features and an overall clinical profile closer to that of 'noAUD' MDD subjects compared to those with alcohol dependence.

Contributors

Jean-Luc Roelandt, Pierre Thomas and Guillaume Vaiva designed the MGHP survey. Imane Benradia and Jean-Luc Roelandt undertook data collection. Louise Carton managed the literature searches. Louise Carton, Benjamin Rolland and Baptiste Pignon wrote the first draft. Baptiste Pignon, Benjamin Rolland and Pierre A. Geoffroy designed and undertook statistical analyses. All authors reviewed and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2018.02.009.

References

Amad, A., Guardia, D., Salleron, J., Thomas, P., Roelandt, J.-L., Vaiva, G., 2013. Increased prevalence of psychotic disorders among third-generation migrants: results from the French mental health in general population survey. Schizophr. Res. 147, 193–195.

Baethge, C., Baldessarini, R.J., Freudenthal, K., Streeruwitz, A., Bauer, M., Bschor, T., 2005. Hallucinations in bipolar disorder: characteristics and comparison to unipolar depression and schizophrenia. Bipolar Disord. 7, 136–145.

Bailey, K., Webster, R., Baker, A.L., Kavanagh, D.J., 2012. Exposure to dysfunctional parenting and trauma events and posttraumatic stress profiles among a treatment sample with coexisting depression and alcohol use problems. Drug Alcohol Rev. 31, 529–537.

Blanco, C., Alegría, A.A., Liu, S.-M., Secades-Villa, R., Sugaya, L., Davies, C., Nunes, E.V., 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, 865–873.

Bradford-Hill, A., 1965. The environment and disease: association or causation? Proc. R. Soc. Med. 58, 295–300.

Brady, K.T., Verduin, M.L., Tolliver, B.K., 2007. Treatment of patients comorbid for addiction and other psychiatric disorders. Curr. Psychiatry Rep. 9, 374–380.

Brière, F.N., Rohde, P., Seeley, J.R., Klein, D., Lewinsohn, P.M., 2014. Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. Compr. Psychiatry 55, 526–533.

Brower, K.J., Aldrich, M.S., Robinson, E.A., Zucker, R.A., Greden, J.F., 2001. Insomnia, self-medication, and relapse to alcoholism. Am. J. Psychiatry 158, 399–404.

Brower, K.J., 2015. Assessment and treatment of insomnia in adult patients with alcohol use disorders. Alcohol Fayetev. 49, 417–427.

Caria, A., Roelandt, J.-L., Bellamy, V., Vandeborre, A., 2010. Mental health in the general population: images and realities (MHGP): methodology of the study. L'Encephale 36, 1–6.

Cohidon, C., 2007. Prévalence des troubles de santé mentale et conséquences sur l'activité professionnelle en France dans l'enquête Santé mentale en population générale: images et réalités [WWW Document]. URL http://opac.invs.sante.fr/doc_num.php?explnum_id=3595 (Accessed 14 May 2017).

Conner, K.R., Duberstein, P.R., 2004. Predisposing and precipitating factors for suicide among alcoholics: empirical review and conceptual integration. Alcohol. Clin. Exp. Res. 28, 6S–17S.

Cornelius, J.R., Salloum, I.M., Mezzich, J., Cornelius, M.D., Fabrega, H., Ehler, J.G., Ulrich, R.F., Thase, M.E., Mann, J.J., 1995. Disproportionate suicidality in patients with comorbid major depression and alcoholism. Am. J. Psychiatry 152, 358–364.

Cornelius, J.R., Salloum, I.M., Day, N.L., Thase, M.E., Mann, J.J., 1996. Patterns of suicidality and alcohol use in alcoholics with major depression. Alcohol. Clin. Exp. Res. 20, 1451–1455.

Cranford, J.A., Nolen-Hoeksema, S., Zucker, R.A., 2011. Alcohol involvement as a function of co-occurring alcohol use disorders and major depressive episode: evidence from the national epidemiologic survey on alcohol and related conditions. Drug Alcohol Depend. 117, 145–151.

Davis, L.L., Rush, J.A., Wisniewski, S.R., Rice, K., Cassano, P., Jewell, M.E., Biggs, M.M., Shores-Wilson, K., Balasubramani, G.K., Husain, M.M., Quitkin, F.M., McGrath, P.J., 2005. Substance use disorder comorbidity in major depressive disorder: an exploratory analysis of the sequenced treatment alternatives to relieve depression cohort. Compr. Psychiatry 46, 81–89.

Davis, L.L., Frazier, E., Husain, M.M., Warden, D., Trivedi, M., Fava, M., Cassano, P., McGrath, P.J., Balasubramani, G.K., Wisniewski, S.R., Rush, A.J., 2006. Substance use disorder comorbidity in major depressive disorder: a confirmatory analysis of the

STAR*D cohort. Am. J. Addict. 15, 278–285.

Davis, C.G., Thake, J., Vilhena, N., 2010. Social desirability biases in self-reported alcohol consumption and harms. Addict. Behav. 35, 302–311.

Dawson, D.A., Grant, B.F., Stinson, F.S., Chou, P.S., 2005. Psychopathology associated with drinking and alcohol use disorders in the college and general adult populations. Drug Alcohol Depend. 77, 139–150.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2009. Tests of causal links between alcohol abuse or dependence and major depression. Arch. Gen. Psychiatry 66, 260–266.

Fountoulakis, K.N., Iacovides, A., Gerasimou, G., Fotiou, F., Ioannidou, C., Bascialla, F., Grammaticos, P., Kaprinis, G., 2004. The relationship of regional cerebral blood flow with subtypes of major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 28, 537–546.

Fuehrlein, B.S., Mota, N., Arias, A.J., Trevisan, L.A., Kachadourian, L.K., Krystal, J.H., Southwick, S.M., Pietrzak, R.H., 2016. The burden of alcohol use disorders in U.S. military veterans: results from the national health and resilience in veterans study. Addiction 111, 1786–1794.

Furukawa, T.A., Konno, W., Morinobu, S., Harai, H., Kitamura, T., Takahashi, K., 2000. Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression. Psychiatry Res. 96, 211–220.

Geoffroy, P.A., Hoertel, N., Etain, B., Bellivier, F., Delorme, R., Limosin, F., Peyre, H., 2017. Insomnia and hypersomnia in major depressive episode: prevalence, socio-demographic characteristics and psychiatric comorbidity in a population-based study. J. Affect. Disord. 226, 132–141.

Gilman, S.E., Abraham, H.D., 2001. A longitudinal study of the order of onset of alcohol dependence and major depression. Drug Alcohol Depend. 63, 277–286.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645.

Grant, B.F., Harford, T.C., 1995. Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug Alcohol Depend. 39, 197–206.

Grant, B.F., Goldstein, R.B., Saha, T.D., Chou, S.P., Jung, J., Zhang, H., Pickering, R.P., Ruan, W.J., Smith, S.M., Huang, B., Hasin, D.S., 2015. Epidemiology of DSM-5 alcohol use disorder. JAMA Psychiatry 72, 757–766.

Green, A.I., Brown, E.S., 2006. Comorbid schizophrenia and substance abuse. J. Clin. Psychiatry 67, e08.

Grolleau, A., Cougnard, A., Bégaud, B., Verdoux, H., 2008. Congruence between diagnosis of recurrent major depressive disorder and psychotropic treatment in the general population. Acta Psychiatr. Scand. 117, 20–27.

Hasin, D.S., Goodwin, R.D., Stinson, F.S., Grant, B.F., 2005. Epidemiology of major depressive disorder: results from the national epidemiologic survey on alcoholism and related conditions. Arch. Gen. Psychiatry 62, 1097–1106.

Hasler, G., Drevets, W.C., Manji, H.K., Charney, D.S., 2004. Discovering endophenotypes for major depression. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 29, 1765–1781.

Lamboy, B., Léon, C., Guilbert, P., 2007. Depressive disorders and use of health services in the French population according to the health barometer 2005. Rev. Epidemiol. Sante Publique 55, 222–227.

Le Pape, A., Lecomte, T., 1999. Prévalence et prise en charge médicale de la dépression. France 1996–1997. | Base documentaire | BDSP [WWW Document]. URL http://www.bdsp.ehesp.fr/Base/227342/ (Accessed 06 May 2017).

Leray, E., Camara, A., Drapier, D., Riou, F., Bougeant, N., Pelissolo, A., Lloyd, K.R., Bellamy, V., Roelandt, J.L., Millet, B., 2011. Prevalence, characteristics and co-morbidities of anxiety disorders in France: results from the mental health in general population survey (MHGP). Eur. Psychiatry J. Assoc. Eur. Psychiatr. 26, 339–345.

Leventhal, A.M., Francione Witt, C., Zimmerman, M., 2008. Associations between depression subtypes and substance use disorders. Psychiatry Res. 161, 43–50.

Leventhal, A.M., Gelernter, J., Oslin, D., Anton, R.F., Farrer, L.A., Kranzler, H.R., 2011. Agitated depression in substance dependence. Drug Alcohol Depend. 116, 163–169.

Lin, C.-H., Chen, Y.-S., Lin, C.-H., Lin, K.-S., 2007. Factors affecting time to re-hospitalization for patients with major depressive disorder. Psychiatry Clin. Neurosci. 61, 249–254.

Lunsford, T., Lunsford, B., 1995. The Research Sample, Part I: Sampling.: JPO: Journal of Prosthetics and Orthotics [WWW Document]. LWW. URL http://journals.lww.com/jpojournal/Fulltext/1995/00730/The_Research_Sample_Part_I_Sampling_.8.aspx (Accessed 09 April 2017).

Morojele, N.K., Saban, A., Seedat, S., 2012. Clinical presentations and diagnostic issues in dual diagnosis disorders. Curr. Opin. Psychiatry 25, 181–186.

Pacek, L.R., Martins, S.S., Crum, R.M., 2013. The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J. Affect. Disord. 148, 188–195.

Pignon, B., Geoffroy, P.A., Thomas, P., Roelandt, J.-L., Rolland, B., Morgan, C., Vaiva, G., Amad, A., 2017a. Prevalence and clinical severity of mood disorders among first-, second- and third-generation migrants. J. Affect. Disord. 210, 174–180.

Pignon, B., Schürhoff, F., Szöke, A., Geoffroy, P.A., Jardri, R., Roelandt, J.-L., Rolland, B., Thomas, P., Vaiva, G., Amad, A., 2017b. Sociodemographic and clinical correlates of psychotic symptoms in the general population: findings from the MHGP survey. Schizophr. Res. http://dx.doi.org/10.1016/j.schres.2017.06.053. Epub ahead of print.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L., Goodwin, F.K., 1990. Comorbidity of mental disorders with alcohol and other drug abuse: results from the epidemiologic catchment area (ECA) study. JAMA 264, 2511–2518.

Rodgers, S., Grosse Holtforth, M., Müller, M., Hengartner, M.P., Rössler, W., Ajdacic-Gross, V., 2014. Symptom-based subtypes of depression and their psychosocial correlates: a person-centered approach focusing on the influence of sex. J. Affect. Disord. 156, 92–103.

Rolland, B., Geoffroy, P.-A., Pignon, B., Benradia, I., Font, H., Roelandt, J.-L., Amad, A., 2017. Alcohol use disorders and immigration up to the third generation in France: findings from a 39,617-subject survey in the general population. Alcohol. Clin. Exp. Res. 41, 1137–1143.

Schuch, J.J.J., Roest, A.M., Nolen, W.A., Penninx, B.W.J.H., de Jonge, P., 2014. Gender differences in major depressive disorder: results from the Netherlands study of depression and anxiety. J. Affect. Disord. 156, 156–163.

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M., Dunbar, G., 1997. The validity of the mini international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry 12, 232–241.

Sher, L., Oquendo, M.A., Galfalvy, H.C., Grunebaum, M.F., Burke, A.K., Zalsman, G., Mann, J.J., 2005. The relationship of aggression to suicidal behavior in depressed patients with a history of alcoholism. Addict. Behav. 30, 1144–1153.

Sher, L., Stanley, B.H., Harkavy-Friedman, J.M., Carballo, J.J., Arendt, M., Brent, D.A., Sperling, D., Lizardi, D., Mann, J.J., Oquendo, M.A., 2008. Depressed patients with co-occurring alcohol use disorders: a unique patient population. J. Clin. Psychiatry 69, 907–915.

Smith, S.M., Goldstein, R.B., Grant, B.F., 2016. The association between post-traumatic stress disorder and lifetime DSM-5 psychiatric disorders among veterans: data from the national epidemiologic survey on alcohol and related conditions-III (NESARC-III). J. Psychiatr. Res. 82, 16–22.

Suttajit, S., Kittirattanapaiboon, P., Junsirimongkol, B., Likhitsathian, S., Srisurapanont, M., 2012. Risks of major depressive disorder and anxiety disorders among Thais with alcohol use disorders and illicit drug use: findings from the 2008 Thai national mental health survey. Addict. Behav. 37, 1395–1399.

Tebeka, S., Pignon, B., Amad, A., Le Strat, Y., Brichant-Petitjean, C., Thomas, P., Vaiva, G., Roelandt, J.-L., Benradia, I., Etain, B., Rolland, B., Dubertret, C., Geoffroy, P.A., 2018. A study in the general population about sadness to disentangle the continuum from well-being to depressive disorders. J. Affect. Disord. 226, 66–71.

Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., STROBE Initiative, 2007. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335, 806–808.

Yoon, Y.-H., Chen, C.M., Yi, H.-Y., Moss, H.B., 2011. Effect of comorbid alcohol and drug use disorders on premature death among unipolar and bipolar disorder decedents in the United States, 1999 to 2006. Compr. Psychiatry 52, 453–464.

Yoon, G., Petrakis, I.L., Rosenheck, R.A., 2015. Correlates of major depressive disorder with and without comorbid alcohol use disorder nationally in the veterans health administration. Am. J. Addict. 24, 419–426.

Zhabenko, O., Krentzman, A.R., Robinson, E.A.R., Brower, K.J., 2013. A longitudinal study of drinking and depression as predictors of insomnia in alcohol-dependent individuals. Subst. Use Misuse 48, 495–505.