Cross-analysis of Depression with Alcohol and Drug Abuse: A Systematic Review

Lixin Chen[1, a, †], Yanchen Chen[2, †], Yuhong Fu[3, †]

[1]*School of Pharmaceutical Sciences, Jilin University, Changchun, Jilin, China*

[2]*Immaculate High School, Immaculate High School, CT, United State*

[3]*The University of Adelaide, Adelaide, South Australia 5005, Australia*

[a)]Corresponding author email: clx18@mails.jlu.edu.cn

[†]These authors contributed equally.

Keywords: Cross-analysis, Depression, Alcohol and Drug Abuse.

Abstract: Alcohol use, drug abuse, with depressive disorders are commonly co-occurred more often than expected by chance, requires more attention paid to health concerns of these groups of people. We thus presented a systematic review to characterize depressive disorders and provide cross-analysis results summarized for depression with alcohol and drug abuse. The findings suggest that people who used alcohol or drugs have a moderately increased risk of depression later in life. Our findings contribute to strengthening the damaging effects of substances and alcohol abuse, also considering the public health impacts of depression and depressive symptoms.

1. Depressive Disorder

Depression is a quite common mental illness. It is estimated that 350 million people suffer from depression worldwide. Chronic moderate or severe depression can become a serious illness. Patients can be clinically disproportionate to their situation and suffer from depression, ranging from moping to sadness, low self-esteem, depression, and even pessimism. It is estimated that up to 1 million people die by suicide each year due to depression.

1.1 Types of Depression

Depression can be roughly divided into three categories: major depressive disorder, persistent depressive disorder, and seasonal affective disorder.

Major depressive disorder (MDD), a psychiatric disorder, is often accompanied by a lack of energy, a lack of interest in general leisure activities, unexplained pain, and low self-esteem. Patients may have delusions or experience hallucinations. Such symptoms often last for two weeks or more. The episodes of major depression are not continuous but may last for several years, with a few moments of normalcy, but most of the time in a depressed state. Major depression can harm daily life, work, education, sleep, eating habits, and overall health. MDD can occur when people's constitution (excessive emotional vulnerability) and external stressors come together.

The second type is Persistent Depressive Disorder (PDD), which is less severe than MDD but lasts longer. PDD is characterized by prolonged mood disorders that are not easily controlled, and it occurs with at least two of the following: feelings of disappointment, insomnia or narcolepsy, poor concentration or difficulty making decisions, insufficient energy or fatigue, poor self-esteem, low appetite, or excessive eating. People with chronic depression are more likely than the general population to develop an MDD. Fluctuations in symptoms may lead to episodes of major depression over time. This condition is sometimes called ‘double depression.’

The last type is Seasonal Affective Disorder (SAD). Most people with SAD remain healthy for most of the year but have symptoms in the winter or summer. However, SAD is notable in areas of 30 degrees north latitude or 30 degrees south latitude. Most of the symptoms are accompanied by a loss of emotional control or regularization. The symptoms of SAD are the same as PDD or Clinical

depression, and sometimes the person may not feel depressed, but somewhat unable to get up and do things.

1.2 Treating Options

1.2.1 Major Treatments for MDD

For MDD, there are three treatments: psychotherapy, pharmacotherapy, and electroconvulsive therapy.

Psychotherapy can be one-to-one or one-to-many. It can be administered by psychotherapists, psychiatrists, psychologists, outpatient social workers, counsellors, and psychiatric nurses. Among psychotherapists, cognitive behavioural therapy, a psychotherapeutic orientation, is a talk therapy that addresses disabling emotional, behavioural, and cognitive problems in a goal-oriented and systematic process. Any therapy that is based on a combination of basic behavioural and cognitive research can be called "Cognitive Behavioural Therapy". This is the most widely used therapy for people with psychiatric disorders. Unlike medication, cognitive behavioural therapy can only be used to treat milder mental illnesses and has limited effect on more severe cases such as anxiety, major depression, and obsessive-compulsive disorder. [1]

The effectiveness of prescription pharmacotherapy can be compared to psychotherapy, but more patients discontinue medication early due to side effects than psychotherapy. Usually, to reduce side effects, physicians will adjust the dosage of the medication according to the severity of the patient's symptoms or mix it with several different medications. [2]

Electroconvulsive therapy refers to the treatment of psychiatric disorders by inducing spasticity through electric shocks to the brain. It is used in psychiatry to treat a severe major depressive disorder, bipolar disorder, and schizophrenia, especially when all medications and psychotherapy have failed. The forms of electrotherapy can be broadly distinguished as bilateral and unilateral electrotherapy, and bilateral electrotherapy can be subdivided into bilateral temporal lobe and bilateral frontal lobe electroconvulsive therapy. In bilateral temporal lobe electrotherapy, the electric current is passed through the temporal lobe of the brain bilaterally to achieve the healing effect, and the electric shocks are placed on both sides of the head. Unilateral therapy mostly places the electric shocks on the right temporal lobe. Common side effects after electrotherapy include transient confusion and retrospective memory loss, in addition to muscle aches and headaches due to muscle twitching, but these discomforts are mostly relieved by medication. [3]

1.2.2 Major Treatments for PDD

For PDD, there are generally two types of treatment, namely medication and psychotherapy. Unlike major depressive disorder, medication should only be the last option for the treatment of a chronic depressive disorder. The treatment should mainly be a spiritual therapy that guides the patient to understand the nature of chronic depression and learn to deal with it. Usually, the side effects of medication are nausea, diarrhea, drowsiness, etc. In addition to medication, a combination of medication and psychotherapy may have the best results. The type of psychotherapy that will help the patient is determined by many factors, including the nature of any stressful events, the availability of family and social assistance, and the patient's personal preferences.

1.2.3 Major Treatments for SAD

For SAD, there are no specific treatments that are particularly widely used. However, increasing the amount of outdoor activity and getting more sunshine does provide some relief for SAD symptoms. [4]

2. Depression and alcohol

Depression and alcohol dependence provides an incredibly significant contribution to the incidence of mental illnesses worldwide, and more and more epidemiological studies report that people with alcohol dependence are at higher risk of depression. Depression and alcohol dependence

are diseases caused by a combination of genetics, environment, and individual susceptibility, and they are each other's high-risk factors [5]. The first factor is genetic. A twin study reported [6] that depression and alcohol dependence have a moderate level of genetic responsibility, with a correlation between 0.3 and 0.6. Another study involving molecular genetics also confirmed this conclusion, pointing out that the two have a shared genetic risk, but the genetic correlation mechanism has not yet been elucidated [7]. Similarly, another study exploring the relationship between genes and alcohol addiction and depression found that variants in the muscarinic acetylcholine receptor M2 (CRHM2) gene led to an increased risk of alcohol addiction and drug addiction and that the interaction between alcohol addiction and drug addiction increased the risk of depression [8].

Another possible explanation for the causal relationship between alcohol addiction and depression is that alcohol exposure causes several metabolic changes that increase the risk of developing depression. A study based on a bioinformatics approach suggests that alcohol exposure leads to a decrease in the production of methylenetetrahydrofolate reductase (MTHFR). The amount of this enzyme secreted is closely related to the level of folate in the body, and when MTHFR is reduced, the level of folate also decreases, which further leads to an increased risk of depression [7]. In addition to this, the act of drinking alcohol can alter the composition and activity of the intestinal flora, while Cryan and Dinan[9] mentioned pathways under the gut-brain axis involving pro-inflammatory cytokines and tryptophan metabolism, which was shown to be strongly associated with the production of depressive behaviors, as well as the production of several neurotransmitters (serotonin, GABA, dopamine, acetylcholine) by intestinal bacteria, but when drinking behavior occurs, the function of the gut flora to secrete these neurotransmitters is impaired, which further promotes the production of depressive behavior.

A third explanation for the causal relationship between alcohol addiction and depression is that alcohol abuse may adversely affect an individual's financial, legal status, and multiple social lives, such as building intimate relationships, which in turn increases the risk of depressive behaviors emerging. Alcohol addiction has been shown to decrease life quality [10]. Fergusson, Boden, and Horwood [11] suggest that after reducing the effects of confounding factors, changes in life circumstances can still affect both alcohol intake and the emergence of depressive behaviors. Further, when alcohol addiction symptoms are further exacerbated, the resulting unemployment, family breakdown, employment difficulties, legal disputes, and physical impairment can induce more severe depression.

After analysing the causal relationship between alcohol addiction and depression, these findings can guide treatment options for patients with alcohol addiction combined with depression to some extent in the clinical treatment and public health fields. Because of the strong causal link between the two, some studies have found more limited relief of alcohol addiction symptoms in some patients with alcohol addiction comorbid with depression when they receive only depression-specific treatment, while many others have reported that alcohol addiction withdrawal treatment resulted in reduced symptoms of depression [12]. Other studies have reported that a certain percentage of depressed patients choose to use alcohol as a treatment in early self-diagnosis, and while alcohol can provide some relief from depressive symptoms in the early stages. Long-term alcohol use can instead exacerbate depression [13].

This situation suggests that physicians should prioritize the combined treatment of alcohol addiction and depression in the clinical treatment of patients with combined alcohol addiction and depression to achieve better outcomes.

3. Depression and drug use

MDD is often accompanied by drug abuse or dependence, henceforth referred to as substance use disorders (SUDs, excluding nicotine and caffeine). The mental health field has long debated whether these conditions are independently occurring disorders or are overlapping illnesses, intertwined by common etiologic and vulnerability factors. The initial presentation of depression can be obscured by the overriding symptoms or side effects of a SUD. Clinicians are reluctant to treat depression in a

patient with a SUD, often requiring sustained sobriety prior to initiating antidepressant treatment. Treatment outcomes in patients who are dually diagnosed lack validation owing to limited systematic research. Most studies involve the treatment of MDD, excluding patients with recent SUDs. Some conducted studies have shed some light on these issues recently [13].

The prevalence of drug abuse in mood disorders (other than alcohol and nicotine) is estimated to be 19.4% (lifetime prevalence), and the presence of drug abuse increases the risk for depression by a factor of almost 5 (odds ratio [OR] = 4.7) (Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study) [14]. Within the subtypes of mood disorders, the comorbidity rates are highest for bipolar I (40.7%, OR= 11). For major depressive disorder (MDD), the prevalence estimates from the most recent national survey were 24% [15].

Comorbidity of cannabis abuse and depression is also relatively common [16]. Like nicotine, it is speculated that cannabis abusers might be attempting to self-medicate their dysphoria. It is also possible that chronic cannabis abuse triggers depression [17]. Indeed, US National Survey on Drug Use and Health (NSDUH) data revealed that compared to non-users of any illicit drug, the odds of past-year MDE among those who used marijuana only, other illicit drugs only, and marijuana and other illicit drugs were 1.54 (95% CI = 1.17–2.03), 2.75 (95% CI = 1.75–4.33), and 2.12 (95% CI = 1.45–3.09), respectively. Those who used marijuana and other drugs also had higher odds (2.44, 95% CI = 1.58–3.77) of suicidal thoughts than non-users of any illicit drug. However, among users of any illicit drug, no difference was found among users of marijuana only, marijuana and other illicit drugs, and other illicit drugs only [18].

Table 1. Characteristics by marijuana and/or other drug use among the 50+ years age group [18]

				MARIJUANA &		
		NO ILLICIT	MARIJUANA	OTHER ILLICIT	OTHER ILLICIT	
	ALL	DRUG USE	ONLY	DRUG	DRUGS ONLY	
N(%)	29,634(100)	27,767(94.13)	984(3.03)	281(0.88)	602(1.97)	P[2]
Demographics and health status						
Age (%)						<0.001
50-64 years	59.53	57.75	89.03	95.93	82.62	
65+ years	40.47	42.25	10.97	4.07	17.38	
Race/ethnicity (%)						<0.001
Non-Hispanic White	76.11	76.12	78.07	74.31	73.61	
Black	9.86	9.76	13.04	13.76	10.99	
Hispanic	8.57	8.67	4.89	7.75	9.48	
Asian	3.52	3.64	0.91	0.06	3.07	
Other	1.94	1.87	3.08	4.11	2.85	
Gender (%)						<0.001
Male	46.52	45.67	62.99	72.26	50.63	
Female	53.48	54.33	37.01	27.74	49.37	
Substance use and mental health status						
Past-year alcohol use (%)	61.56	60.19	87.75	90.97	73.42	<0.001
Past-year alcohol abuse or dependence (%)	3.23	2.47	14.88	26.66	11.09	<0.001

Past-year any drug abuse or dependence (%)	0.58	N/A	4.55	24.58	11.57	<0.001
Past-year marijuana abuse (%)	0.13	N/A	1.91	6.87	N/A	<0.001
Past-year marijuana dependence (%)	0.12	N/A	2.65	6.13	N/A	<0.001
Past-year tobacco product use (%)	23.17	21.31	57.67	68.53	38.82	<0.001
Lifetime MDE (%)	10.81	9.99	21.23	30.56	25.05	<0.001
Past-year MDE (%)	5.20	4.72	10.51	20.21	13.41	<0.001
Past-year serious suicidal thoughts (%)	2.48	2.21	5.0	13.64	6.43	<0.001
Past-year suicide plans among ideators[3] (%)	28.02	27.23	22.52	39.60	36.66	0.331
Past-year suicide attempt among ideatorsc (%)	11.53	11.37	4.90	20.88	13.14	0.281

In an analysis of Lebanese Medical students during the 4 years of medical school, 23.8% of medical students reported depressive symptomatology, with 14.5% having suicidal ideations. Forty-three percent were found to have burnout. Those who screened positive for burnout were more likely to be males. Except for burnout, there was no significant difference in the prevalence of depression or anxiety among the 4 years of medical school. There was a significant difference in alcohol use, illicit substance use, and marijuana use during the four medical school years. Increased rates of substance use were detected as well as a more tolerant attitude toward substance use in general, specifically cannabis [19].

Table 2. Selected sample characteristics and correlation with depressive symptoms and burnout [19]

Variable	N=172	Depressive symptoms (%)	p value
Age(years)			0.44
20-25	75	26.7	
>25	97	21.6	
Sex			0.01
Male	88	13.6	
Female	84	34.5	
Relationship status			0.69
Single	169		
Married	3		
Year of medical school			0.81
I	39	28.2	
II	30	26.7	
III	54	22.2	
IV	49	20.4	
Living arrangement			0.51
With parents	104	22.1	
On-campus	68	26.5	
History of suicide attempt			0.00
Yes	8	62.5	
No	164	22.0	
Sleep duration			0.04
Less than 6 h	73	31.5	
More than 6 h	99	18.2	

Table 3. Odds ratio (OR) of factors associated with burnout among medical students(N=172) [19]

Variable	OR	95%(CI)	
		Lower	Upper
Gender (female versus male)*	1.928403	1.045878	3.555613
Age group (20-25 versus 25 and above)	1.073171	0.584036	1.97195
Illicit drugs ever use (yes versus no)	1.392832	0.740528	2.619724
History of suicidal attempt or self-harm (yes versus no)	4.235294	0.829672	21.62025
Marijuana use (yes versus no)	0.731616	0.385010	1.390254
Nonprescribed sedatives or benzodiazepines use (yes versus no)*	0.413174	0.344853	0.495030
Stimulant use (yes versus no)	0.741935	0.206676	2.663434

In an average follow-up period of 44 years survey, 4500 men were diagnosed with or treated for depression at a mean age of 54 years. Independent associations with an increased risk of depression were found for the use of drugs at least once (aHR 1.21, 95 % CI 1.10–1.32, $p < 0.001$) and >50 times (aHR 1.48, 95 % CI 1.23–1.77, $p < 0.001$) and the use of inhalants (aHR 1.16, 95 % CI 1.05–1.29). Excessive alcohol intake was not associated with the risk of depression [20].

Table 4. Characteristics of substance use in the study cohort [20]

	Total sample (n=24,564)	Depressed (n=4500)	Non-depressed (n=20,064)	X^2, df	P
Inhalants					
Frequency of inhalant consumption			X^2=20.72, df=3	<0.001***	
More than 10 times	443(1.8%)	92(2.1%)	341(1.7%)		
2-10 times	1034(4.3%)	218(5.0%)	816(4.2%)		
One time	1959(8.2%)	414(9.4%)	1545(7.9%)		
Never	20,584(85.7%)	3671(83.4%)	19,615(86.2%)		
Drugs					
Tried drugs			X^2=27.46, df=1	<0.001***	
Yes	2758(12.2%)	601(14.6%)	2121(11.6%)		
No	19,778(87.8%)	3507(85.4%)	16,147(88.4%)		
Frequency of drug consumption			X^2=39.86, df=5	<0.001***	
More than 50 times	486(2.0%)	126(2.8%)	360(1.8%)		
11-50 times	456(1.9%)	94(2.1%)	362(1.8%)		
5-10 times	460(1.9%)	117(2.6%)	343(1.7%)		
2-4 times	802(3.3%)	168(3.7%)	634(3.2%)		
1 time	1072(4.4%)	186(4.1%)	886(4.4%)		
Never	21,286(86.7%)	3808(84.6%)	17, 478(87.1%)		
Drug consumption desire			X^2=7.98, df=2	0.02*	
Often	96(0.5%)	20(0.6%)	76(0.5%)		
Sometimes	1740(9.0%)	350(10.2%)	1380(8.7%)		
Never	17,530(90.5%)	3060(89.2%)	14, 359(90.8%)		
*P<0.05%, **P<0.01, ***P<0.001					

4. Conclusion

Although the studies described above combined comorbid alcohol use disorders and illicit drug use disorders, these should not necessarily be regarded as equivalent. There may be differences in the clinical features and outcome of depressed individuals with alcohol vs. drug use disorders yet to be determined in larger studies.

The present study suggests that alcohol and drug abuse in young adulthood and old men are moderately associated with the risk of depression later in life among men. The use of drugs and inhalants was also associated independently with the risk of depression, although the societal impact of such substance use is smaller, given its lower prevalence. The findings suggest that people who reported to have used alcohol or drugs have a moderately increased risk of depression later in life. These results contribute to strengthening the existing literature on the damaging effects of substances and alcohol abuse, also considering the public health impacts of depression and depressive symptoms.

References

[1] Cuijpers, P., A. van Straten, and F. Smit, Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. International Journal of Geriatric Psychiatry, 2006. 21 (12): p. 1139 - 1149.

[2] Cuijpers, P., et al., Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. 2008.

[3] Horne, R.L., et al., Comparing bilateral to unilateral electroconvulsive therapy in a randomized study with EEG monitoring. 1985. 42 (11): p. 1087 - 1092.

[4] Partonen, T. and J. J. C. d. Lönnqvist, Seasonal affective disorder. 1998. 9 (3): p. 203 - 212.

[5] Boden, J. M. and D. M. J. A. Fergusson, Alcohol and depression. 2011. 106 (5): p. 906 - 914.

[6] Kendler, K.S., et al., Alcoholism and major depression in women: a twin study of the causes of comorbidity. 1993. 50 (9): p. 690 - 698.

[7] Almeida, O.P., et al., The triangular association of ADH1B genetic polymorphism, alcohol consumption and the risk of depression in older men. 2014. 19 (9): p. 995 - 1000.

[8] Luo, X., et al., CHRM2 gene predisposes to alcohol dependence, drug dependence and affective disorders: results from an extended case–control structured association study. 2005. 14 (16): p. 2421 - 2434.

[9] Dinan, T.G., J.F.J.N. Cryan, and Motility, Melancholic microbes: a link between gut microbiota and depression? 2013. 25 (9): p. 713 - 719.

[10] Foster, J., et al., Quality of life in alcohol-dependent subjects–a review. 1999. 8 (3): p. 255 - 261.

[11] Fergusson, D. M., J. M. Boden, and L. J. J. A. o. g. p. Horwood, Tests of causal links between alcohol abuse or dependence and major depression. 2009. 66 (3): p. 260 - 266.

[12] Grant, V. V., S. H. Stewart, and C. D. J. P. o. a. b. Mohr, Coping-anxiety and coping-depression motives predict different daily mood-drinking relationships. 2009. 23 (2): p. 226.

[13] Davis, L., et al., Major depression and comorbid substance use disorders. 2008. 21 (1): p. 14 - 18.

[14] Regier, D.A., et al., Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. Jama, 1990. 264 (19): p. 2511 - 8.

[15] Rovner, B. and R.J.E.-B.O. Casten, The epidemiology of major depressive disorder. 2003. 4 (4): p. 186 - 187.

[16] Bovasso, G. B. J. A. J. o. P., Cannabis abuse as a risk factor for depressive symptoms. 2001. 158 (12): p. 2033 - 2037.

[17] Volkow, N. D. J. B. p., The reality of comorbidity: depression and drug abuse. 2004. 56 (10): p. 714 - 717.

[18] Choi, N.G., et al., Relationship between marijuana and other illicit drug use and depression/suicidal thoughts among late middle-aged and older adults. 2016. 28 (4): p. 577.

[19] Talih, F., et al., Examining burnout, depression, and attitudes regarding drug use among Lebanese medical students during the 4 years of medical school. 2018. 42 (2): p. 288 - 296.

[20] Gentile, A., et al., Use of alcohol, drugs, inhalants, and smoking tobacco and the long-term risk of depression in men: A nationwide Swedish cohort study from 1969 – 2017. 2021. 221: p. 108553.