

## A Case Report of Cannabis Induced-Psychotic Depression With Suicidality in a Bisexual 23-Year Old Female Theatre Arts Student of the University of Port Harcourt, Nigeria

Nkporbu AK<sup>1\*</sup>, Ejele O<sup>2</sup> and Orovwigho A<sup>3</sup>

<sup>1</sup>Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

<sup>2</sup>Department of Community Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

<sup>3</sup>Federal Neuropsychiatric Hospital, New Haven, Enugu, Nigeria

\*Corresponding author: Nkporbu AK, Department of Neuropsychiatry, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria, Tel: 8036772778; E-mail: [nakpigi2008@yahoo.com](mailto:nakpigi2008@yahoo.com)

Received Date: 11 July, 2018; Accepted Date: 23 August, 2018; Published Date: 28 August, 2018

Copyright: © 2018 Nkporbu AK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

**Background:** Use of psychoactive substances is now known as one of the biological causes of mental disorders. The case of induced-psychotic depression in a 23-year old female patient who became addicted to cannabis was documented as an example of a biological cause of mental illnesses. The overall clinical scenerio forms this case report. **Aim:** The aim of this report was to highlight a case of cannabis induced-psychotic depression in a 23-year old female patient managed at the Neuropsychiatric ward of UPTH. **Methodology:** The case report of the patient was retrieved and reviewed together with relevant literatures. Ethical approval was gotten from the Ethical Committee of the Hospital. **Results:** A 23-year old female bisexual patient who was diagnosed of Cannabis-induced psychotic depression. Her academic programme was disrupted and she attempted suicide during the psychotic episode. There was no family history of mental illness nor psychoactive substance abuse and she was not a known psychiatric patients and patient has not had any psychiatry consultation prior to this time. Detailed evaluation was made including mental state and physical examinations, routine and other investigations. Patient was managed on admission and her clinical condition improved markedly after two weeks following both pharmacological and brief psychosocial intervention, and was later referred on request. **Conclusion:** Clinicians should always look out for co-morbid substance use disorders and managed accordingly to enhance the patient optimal care.

**Keywords:** Cannabis; Psychotic depression; Suicidality; Student

### Introduction

Before now mental disorders were largely thought to be due to spiritual forces, however, with the advent of medical research, this thinking has significantly changed over the years as there are now evidence-based findings of biological, psychological, social and environmental causes of mental illnesses. Psychoactive substance use is currently one of the major health problems world over [1]. Substance use disorders constitute a serious health burden second to cardiovascular disease [1,2]. The abuse of psychoactive substance including prescription drugs continues to be a major health problems globally [3]. The United Nations Office on Drugs and Crime (UNODC) reports that approximately 5 per cent of the world's population used an illicit drug in 2010 and 27 million people, or 0.6 per cent of the world's population, can be classified as problem drug users [3]. It is estimated that alcohol abuse causes about 2.5 million deaths per year and that heroin, cocaine and other drugs are responsible for 0.1 to 0.2 million deaths per year [3]. In addition to causing death, substance abuse is also responsible for significant morbidity and the treatment of drug addiction creates enormous burden on families and the society [4,5].

Different types of psychoactive substances are consumed and there are evidence of new emerging substances in different regions of the world [6]. Psychoactive substance use is prevalence among age 12-64, reported to be most prevalent among the youths and adolescents [3,6]. Existing studies have found a correlation between adolescent substance

abuse and becoming a problem drinker [7,8]. Also, accidental and intentional fatalities that are associated with drug use form one of the leading preventable causes of death for the 15-24-year-old population [9]. Drug abuse in the adolescent population carries a high risk for school underachievement, delinquency and other behavioural deviations, teenage pregnancy, common mental disorders particularly depression and anxiety disorders [8].

Substance use disorders have remained on the increase among young people particularly in the tertiary institutions for various reasons ranging from the 'high', alertness, motivation, increased performance, conform to group norms, curiosity and experimentation, rise of cultism and rival groups to mention a few [9,10]. Substance-induced mental disorders could arise from substance use and some substance abusers can also present with co-occurring mental disorders [3,11]. Substance use has been associated with suicide either mediated by psychosocial factors or through mental disorders particularly depression acting as intermediary. Therefore, the presence of both substance abuse and depression will further increase the risk of suicide.

Before now, substance use has been reported to be more among the males, but current researches have reported a narrowing of the gap [12-14]. This may be due to increased awareness and desire to assume more gender roles by women and peer pressure [12-14]. Also, women were more unlikely to report substance use disorder due to cultural reasons, however awareness is gradually changing the scenario [12].

The fact that more gender sensitive treatment facilities have become available has equally contributed to the closing gap because more women are been seen and become available for statistical inclusion [15,16].

Cannabis is among the most commonly consumed psychoactive drug globally alongside alcohol [3]. The behavioural and psychological manifestations developed following regular and increased use of cannabis are amenable to management and usually improve following abstinence. Again, the gap between men and women for cannabis use is gradually reducing [12]. Due to enlightenment and constant drive for gender equality, females are beginning to have more initial opportunities to use cannabis and now tend to start the use at a younger age (16.4 years vs 17.6 years) [17].

There is a higher prevalence of abuse of the prescription drugs by women, particularly the opioid medications [18]. The analgesic property seems to be the major reason for the use. Differences in gender in prescription opioid use has also been noted to occur within specific age groups. A study found that women aged 12 to 17 years had higher rates than men, but that men aged 18 to 25 years had higher rates than women [19]. Gender differences in reason for use and aberrant drug-taking behaviors have also been observed. McCabe and colleagues found that among college students, men were significantly more likely than women to use prescription opioids for experimentation (35.3% vs 18.4%) or to get high (39.4% vs 24.4%) [20]. A study of chronic pain patients found that women were significantly more likely than men to hoard unused medications and to use additional drugs (eg, sedatives) to enhance the effectiveness of prescription opioids [21]. The use of prescription opioids has soared in the past 2 decades. For example, from 1992 to 2003, a 141% increase in prescription opioid abuse was reported [20]. Two large epidemiological surveys found that women engage in the nonmedical use of prescription opioids more often than men [18].

It has been documented that female tend to manifest faster with the adverse consequences of substance use than male [22-24]. Compared with men, women experience significantly shorter time intervals between the initiation of substance use and the onset of significant substance-related problems and treatment entry [24]. This differential accelerated course, known as telescoping, may be attributed to a variety of unique biological, socioeconomic, psychological, and cultural factors that affect women. For instance, women may be more moderately to severely adversely affected by alcohol use because of the lower percentage of total body water, decreased first pass metabolism because of lower levels of alcohol dehydrogenase in the gastric mucosa, and slower rates of alcohol metabolism when compared with men [25,26].

Gender differences in motives for substance use have been observed, with women being more likely than men to use in response to stress and negative emotions [27]. In contrast, men seem more likely than women to consume substance to enhance positive emotions or to conform to a group [26]. Women with substance-use disorders are significantly more likely to have co-occurring psychiatric disorders that may serve to impede substance-use treatment efforts [27-30]. Such co-occurring disorders may include depression, anxiety disorders, post traumatic disorders, sleep disorders and psychotic disorders.

Few investigations have examined gender differences in response to psychotherapeutic or pharmacotherapeutic treatments for mood and anxiety disorders among individuals with co-occurring substance-use disorder [31-36]. Studies examining agents targeting substance use,

such as naltrexone or disulfiram, as add on treatment of individuals with co-occurring or substance induced mood or anxiety disorders have shown that the agents are under-explored. Thus, prevention and treatment intervention efforts including provision of facility should incorporate these gender differences in management of co-occurring or substance-induced psychiatric conditions to enhance effectiveness and quality of life. The case report below exemplifies a female with substance induced-mental disorders.

## Case Report

Miss U.C. is a 23-yr old female undergraduate, who resides at Aluu Town. She is Catholic and from the Igbo Extraction of Nigeria. She was referred from the Accident and Emergency Unit of the University of Port Harcourt Teaching Hospital to the Neuropsychiatry Department after a 24-hour stabilization. The patient and her friends provided the information.

Problem started about 3 years ago when she was introduced to cannabis by her friends. She started by smoking two drags from a friend's stick, which made her feel really good. She continued and gradually increased her intake to one/two sticks per day initially, and is currently on 3 sticks daily. She had to increase the amount smoked at each time in order to achieve desired effects she usually gets from lower quantities. She has made several failed attempts to stop using the cannabis in the past. She also uses alcohol occasionally, claimed she does not derive any specific benefit from alcohol and has not had reason to drink excessive quantity.

She was introduced to codeine and rohypnol about two years ago by the same friends. She also takes codeine occasionally, about 50mls mixed with juice, once or twice a month. She takes ½-1 tab of rohypnol once a month. She claims to take these to slow down, relax and sleep well.

About 2 days prior to presentation, her friends noticed she was talking irrationally while under the influence of cannabis, as she would start a conversation and veer off. This became increasingly worse over the period preceding presentation. She was also seen to be exhibiting odd behaviours like screaming unnecessarily and singing out loud at the top of her voice even at odd times.

On the eve of her presentation, while under the influence of cannabis, she was involved in a fight with some friends which put her in a state of rage, as she flung things around her room, including her phone and ran outside into an on-coming motorcycle. She was said to have been unconscious for about a minute, but regained full consciousness thereafter and was rushed to the health centre. She also sustained minor injuries to her right thigh. She was immediately referred from the University of Port Harcourt Health Centre to the University of Port Harcourt Teaching Hospital (UPTH) for expert management.

There is a 2-month history of hearing strange voices unheard to others in clear consciousness. The voices tell her she is a failure. She also claims that her friends ganged up against her and they were planning to kill her. Aside this, there were no other thought interference. There is a past history of sustained low mood, low energy, loss of interest in previously pleasurable activities, poor sleep and appetite.

She also reported that on a daily basis she has had difficulty sleeping and concentrating. She has a poor appetite and she describes her mood as continually sad. She reported that she has severally missed her

classes because of extreme weakness and fatigue especially in the morning, and an inability to get herself moving in the morning. These experience have made her lost interest in previously pleasurable activities. She often feels guilty, hopeless and worthless, and had wished to die on many occasions. Her level of concentration has dropped remarkably and often forgets what she has read.

In addition, she had thought of drinking a poisonous substance. She reported that this persistent state of low mood had made her not only continue to use cannabis but also to increase the amount to maintain the usual pleasurable effects. She said cannabis often lifts her mood and helps to keep her going. She has had to engage in spending sprees on few occasions when her mood is high following cannabis use. However there is no elated mood, belief of having extraordinary abilities and no over religiosity. There is a positive history of excessive worrying thoughts, awareness of heartbeat, unexplained fearfulness, and feeling of impending doom. No tremors, excessive sweating or abdominal discomfort. This was her first psychiatry consultation. There was no history of hypertension, diabetes, asthma, epilepsy or sickle cell disease.

She is the 4th of 5 children in a monogamous family setting. Father is a 60yr old retired banker with tertiary level of education. Mother is a 49yr old, gainfully employed in the private sector, with secondary level of education. She is a known PUD, arthritis and glaucoma patient. All the siblings are alive and well adjusted. They live in a 3 bedroom apartment and living conditions are said to be conducive. Relationship with her family members is said to be cordial. There is no family history of mental illness nor substance use disorders.

Her date of birth was 31/07/1994. Her mother had no complication during her pregnancy and birth, and she had a normal childhood development. She had her Nursery and Primary education from 3-11 yrs, and Secondary school from 11-17 yrs both in Lagos, Nigeria. She described herself as an average student. She wrote and passed the West African Examination as well as the Joint Admission Matriculation Board Examination once and passed both. She is currently a final year Theatre Art student, at the University of Port Harcourt. She started noticing a decline in her academic performance since the past one year prior to presentation. She has worked as a marketer for an advert company at the age of 17 years where she received Monthly pay of twenty five thousand naira (N25000).

Her coitarche was at 16yrs of age with her boyfriend of similar age. It was consented but not enjoyable or pleasurable. She is bisexual in orientation and has been since the age of 18yrs. She prefers the female gender as she derives more sexual satisfaction. She meets with males mostly for financial benefits. She is currently in a relationship with an Australian female, who is funding her education currently. They plan to get married soon. They have made plans to settle outside Nigeria and have children via either adoption, sperm donors or surrogacy. She is fully aware of the legal implications with respect to the laws in Nigeria. There was no history of sexual abuse or rape. She presently lives alone in a well ventilated self-contained apartment. She had not had any conflicts with the law. Premorbidly, she liked being with friends and she is quite religious.

Mental State Examination revealed a young female, well kempt and groomed, calm but looks quite confident, very cooperative, responded well to questions asked and maintained good eye contact. No abnormal involuntary motor movements. Her speech was spontaneous, coherent, relevant with normal tone, volume and rate. She described her mood as sad and her affect was depressed. There was no abnormality thought

form, content and possession. There was second person auditory hallucination. Her cognition was fair and she had good test judgement and full insight. Physical examination revealed no abnormality.

A diagnosis of Mental and Behavioural Disorder secondary to polysubstance use, Cannabis dependent (Cannabis-induced mental disorder), and a differential of bipolar affective disorder, depressive phase was made. She was admitted in the Female Psychiatry Ward and placed on appropriate antipsychotic, antidepressant and other medications. Evaluation including detail history, physical and mental state examination, she was admitted into the female Psychiatry Ward. Routine and other investigations including full blood count with differentials, electrolyte, urea and creatinine and urinalysis, thyroid function test done were all within normal ranges. Urine drug toxicology done revealed cannabis to be positive. Clinical management was instituted including pharmacotherapy (detoxification). Psychological treatment was commenced following resolution of the acute phase. She also had supportive psychotherapy and Cognitive Behavioural Therapy.

She spent two weeks on admission in the female mental health ward and made significant improvement as evidenced by resolution of psychotic and other symptoms, improvement in her affect, appetite and sleep, return to full insight and good medication compliance, and adequate personal hygiene. Her parents however requested that she be transferred to Federal Neuropsychiatric Hospital (FNPH) Yaba, Lagos due to proximity to them. She was then discharged on request with a referral letter to FNPH, Yaba, Lagos. A short term follow-up showed that patient became stable overtime and returned to school.

## Discussion

Substance use and abuse world wide is rapidly assuming an epidemic dimension [2,3]. It further become of greater concern among the youths and adolescents [3,6-8]. The tertiary institutions also have provided another vulnerable setting for substance use among the adolescents, because it is basically the first time these young ones would be having this degree of independence and freedom away from their families. This provides ample avenue to explore the many curiosities and hence the experimentation with drugs. The patient in the report was introduced to the different drugs by her friends who were mostly her course mates in the University. Additionally, being a student of Theatre Arts, a Department where a lot of drama plays take place and students may want to boost their performance, may also have contributed to her drug use behaviour. Most times, drugs are used to increase performance and this could apply to theatre Arts students because of the nature of programme they run in the University which often involves role play and performance.

Substances are known to cause variety of substance-induced mental disorders either directly through biological mechanisms or through various degrees of emotional impact of stressful issues on them independently or emanating from substance use [26-29]. Toxic effects of psychoactive substances can mimic psychiatric disorders and make it somewhat difficult to identify the causes of the disorders [37]. Substance-induced disorders are distinct from co-occurring mental disorders and are usually the direct result of the relevant psychoactive substance use, abuse, intoxication or withdrawal [3]. Different individuals vary in the way they respond to substance intoxication or withdrawal [22-24,33]. Patient may have been under intoxication at the point of acting in a rage and fight as she was reported to have just finished using cannabis prior before the altercation with her friend.

Furthermore, either the acute intoxication or hallucinatory voices of the commanding type may have been responsible for the suicide attempt of running into a moving motor cycle. Also, the feeling of hopelessness and worthlessness coupled with evolving awkward behaviours could have also triggered the suicide attempt. Transient death wishes and non-specific suicidal ideation have been reported to be comparatively common during adolescence, and this may be intensified when under influence of psychoactive drug [38].

The patient in the report has no family history of mental illness and there was no history of mental illness prior to use of drugs. To this end, it could be reasonably inferred that her behavioural and psychiatric manifestations were due to the direct effects of drug use. Again, the manifested signs and symptoms are pharmacologically related to cannabis. Suffices to mention that even though the patient was using multiple substance, alcohol, codeine and rohypnol were not consumed to addictive levels.

In the case report, the patient was a young adult of 23 years. The age may be a strong predisposing factor. Many studies have established that drug use is at its peak in the age range of 15-25 years [37]. Gender here is equally another predisposing factor. Before now, considerable gap existed in the prevalence of use of substance in male and females [12,13]. This gap is rapidly closing [12,13]. Awareness and improved societal role play by the women could be responsible. Also more access to healthcare by women has equally increase data gathering, and generally the new wave of curiosity and experimentation among young people may also be another factor. Gender differences in neurochemical adaptations to stress and reward systems may mediate women's susceptibility to drug abuse and further vulnerability to the ensuing effects [27]. Several studies have examined gender differences in stress response and relapse [27,39].

Among substance-dependent subjects, attenuated neuroendocrine stress response in women in the hypothalamo-pituitary-adrenocortical axis has been shown following exposure to stress and drug cues [40]. This hypothalamic-pituitary-adrenocortical (HPA) dysregulation in women may be one key to enhanced vulnerability to stress and subsequent use of substance. Women may often respond to stress and negative affects, as this may be associated with greater emotional intensity at lower levels of HPA arousal [41], by taking to substance use in a bid to achieve emotional stability. Thus, the variable stress of tertiary education program may be responsible for the vulnerability of this female to yield to peer pressure. There was no further information implicating family vulnerability.

It was established that the patient has had to increase the quantity of cannabis over the period of use to sustain desirable effects. This is referred to as tolerance. She has also made several unsuccessful attempts to stop using cannabis particularly following periods of remorse. However, she would usually notice an unpleasant low mood, poor appetite and sleep, irritability and an increased feeling of discomfort. These unbearable withdrawal symptoms would usually stud her motivation and she would eventually go back to using cannabis. The codeine, rohypnol and alcohol were taken occasionally mainly to calm and 'slow' her down, especially when she has become excessively high on cannabis. It therefore appeared she was dependent only on the cannabis.

Several studies have advanced strong relationship between cannabis and mental disorders. Mental disorders can predispose an individual to using cannabis and also cannabis use can cause variety of mental disorders. Clear diagnostic criteria are provided where it is essential to

establish a temporal relationship. In this case report, it was sufficiently establish that cannabis use preceded the behavioural and psychological symptoms the later manifested, the diagnosis of cannabis-induced mental disorder could be glaringly made. Cannabis has an amorphous nature, as a CNS stimulant usually in short-term use and high dose and could also act as a CNS depressant particularly in chronic use [37]. Cannabis can cause both mood as well as psychotic disorders. It primarily acts on the dopaminergic pathway. The patient had florid depressive symptoms with suicidal ideation that were later complicated by psychosis and other irrational behaviours.

Cannabis use has not been found to affect the menstrual phase [42-44], however, cannabis use may help to relieve pain and stabilise mood swing associated with the menstrual cycle for women who have severe premenstrual syndrome or premenstrual dysphoric disorder [44]. Although the patient reported painful menstruation, she did not report that to be the reason for using cannabis. Memory, attention and concentration processes may be affected by marijuana use for up to 7 days following use [45]. The effects of marijuana use on cognitive function and neuropsychological processes may differ by sex. Mental ability, cognitive functions and visual-spatial memory have been found to be impaired [46] among women who smoked heavily, compared with women who were light smokers.

Female tend to manifest earlier with substance use disorders compared to men [21-24]. This has been called the telescoping effects and even though no definitive reason has been given for this difference in gender manifestation, it may be due to the hormonal make up of the women [22]. The patient began to manifest symptoms of drug use about 6 months of heavy use of cannabis. Cannabis pharmacologically enhances dopaminergic activity [37]. With continues and prolonged use of high doses of cannabis, as was the case of the patient in this report, both psychosis as well as acute intoxication are likely to occur. This supports the dopamine theory of schizophrenia and by implication psychosis, a theory that has long been supported by the fact that anti-dopaminergic psychotropic agents can ameliorate psychosis [37]. Thus when the antipsychotic agent olanzapine was instituted in the patient's management, there was resolution of the psychosis and other aberrant symptoms within 2 weeks.

Alcohol acts as a sedative agent at low doses and as a central nervous system depressant at high doses and in long term use. It acts by potentiating GABA neurotransmission [37]. At the long run, alcohol has also been found to affect dopamine and serotonin pathways. This provides some relaxing and initial anxiolytic effects. The sedative and anxiolytic effects provide the rewards and attraction for repeated use especially during periods when she has become very high. Rohypnol is a benzodiazepine which equally offers sedative and anxiolytic effects also by potentiating GABA neurotransmission. Thus this may explain why the patient has been using the medication for its relaxing and calming effects. Benzodiazepine has also been said to have some antipsychotic effects. However, the presence of high dose of a dopaminergic agent like cannabis, the antipsychotic effect of rohypnol may be suppressed. Codeine is a form of opioid and also provides a calming and relaxing mood.

Cannabis use combined with other psychosocial stressors may have been responsible for the affective disorder in this patient [27]. Lifetime rates of mood disorders with or without psychosis are significantly higher among women than men, with and without substance-use disorders [11,28,47]. The 12-month prevalence rates of mood disorders among women with substance-use disorders has been found to be 29.7% [47]. The most common mood disorder among women taking



substances is major depressive disorder (15.4%) [46]. Knowing that there is high prevalence of mood disorder associated with substance use, a comprehensive psychiatric assessment is critical when female addicts present to healthcare facility [48]. Because chronic drug use may enhance vulnerability for these disorders, or lead to organic changes that manifest as a mood or anxiety disorder, careful and detail assessment is necessary to differentiate substance-induced, transient symptoms from a disorder that warrants treatment [48]. One way to do this is to carefully monitor symptoms during a period of abstinence from alcohol or drugs.

It is also very vital to be able to differentiate a substance-induced mental disorder from a co-occurring psychiatric disorder. A family history of mood/psychotic disorders, onset of mood/psychotic symptoms before the onset of the substance-use disorder, and sustained mood/psychotic symptoms during periods of abstinence all point toward an independent mood or psychotic disorder [48]. However, in this patient, there was no family history of either mood or psychotic disorder and symptoms improved easily following few days of medical care and abstinence. Substance –induced mental disorders improve faster compared with co-occurring mental disorders following abstinence from drug. Her bisexual behaviour was seen as her sexual orientation and preference and this according to DSM V diagnostic criteria for sexual disorder is not a disorder itself.

Women are less likely than men to seek treatment, and more likely to encounter gender-specific treatment barriers [31]. Various factors such as child care, financial dependence, and social and cultural stigma, may help explain this finding. To enhance treatment seeking and retention, programs should consider offering childcare, prenatal care, women only treatment, and services specific for women's issues [47]. Interventions specifically designed for women-only groups show promise, indicating that women-only treatment is associated with fewer relapses and higher treatment satisfaction ratings [31,47,49].

Due to the low numbers of women in treatment, few studies have been published regarding gender differences in the effectiveness of treatment of marijuana-use disorders. Research suggests that cognitive behavioral therapy, contingency management treatments, motivational enhancement therapies, treatment of psychiatric manifestation are effective treatments for cannabis dependence [48,50]. However, a limitation of this report is that treatment was truncated by request to refer the patient on the ground of proximity.

## Conclusion

A number of psychoactive substances are known to cause or associate with a variety of mental disorders including psychotic depression. It is therefore important that Clinicians always look out for co-occurring or substance induced mental disorders and managed accordingly to enhance the patient optimal care.

## References

1. Whiteford HA, Degenhardt L, Rehm J, Burstein R, Vos T, et al. (2010) Global burden of disease attributable to mental and substance use disorders: findings from the global burden of disease study. *Lancet* 382: 1575–86.
2. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T (2015) The global burden of mental, neurological and substance use disorders: an analysis from the global burden of disease study 2010. *PloS One* 10: e0116820.
3. United Nations Office on Drugs and Crime (UNODC) (2010) World Drug Report 2010. United Nations Publication, Vienna, Austria.
4. Bloom DE, Cafiero ET, Jane-Llopis E, Abrahams-Gessel S, Bloom LR (2011) The global economic burden of non-communicable diseases. *World Econ Forum*.
5. VicHealth (2007) Mental Health and Wellbeing Research Summary Sheet: Burden of Disease due to mental illness and mental health problems. Res Summ.
6. National Institute on Drug Abuse (NIDA) (2010) A research-based guide for parents, educators and community leaders. Preventing drug use among children and adolescents 2nd edn, Bethesda, Maryland, USA.
7. Belcher HM, Shinitzky HE (1998) Substance abuse in children: prediction, protection and prevention. *Arch Pediatr Adolesc Med* 152: 952-60.
8. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, et al. (2003) Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 111: 564-72.
9. Melchior M, Chastang ZF, Goldberg P, Fombonne E (2008) High Prevalence rates, tobacco, alcohol, and drug use in adolescents and young adults in France: Results from the GAZEL yard study. *Adult Behav* 33: 122-33.
10. Taranian F, Bolhari J, Pairavi H, Tabatabaei MG (2008) The prevalence of drug use among University students in Tehran. *Iranian J. Psychiatry and clinical psychology* 13: 335-42.
11. Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, et al. (2004) Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders on alcohol and related conditions. *Arch Gen Psychiatry* 61: 807–16.
12. Hser YI, Anglin MD, Booth MW (1987) Sex differences in addict careers: 3. *Addiction. Am J Drug Alcohol Abuse* 13: 231–51.
13. Keyes KM, Grant BF, Hasin DS (2008) Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug Alcohol Depend* 93: 21–9.
14. Turner JM, de Wit H (2006) Menstrual cycle phase and responses to drugs of abuse in humans. *Drug Alcohol Depend* 84:1–13.
15. Kaskutas LA, Zhang L, French MT, Witbrodt J (2005) Women's programs versus mixedgender day treatment: results from a randomized study. *Addiction* 100: 60–9.
16. Orwin RG, Francisco L, Bernichon T (2001) Center for Substance Abuse Treatment. Effectiveness of women's substance abuse treatment programs: a meta-analysis. SAMHSA, Arlington, Virginia, United States.
17. Van Etten ML, Anthony JC (1999) Comparative epidemiology of initial drug opportunities and transitions to first use: marijuana, cocaine, hallucinogens, and heroin. *Drug Alcohol Depend* 4: 117-25.
18. Simoni-Wastila L, Ritter G, Strickler G (2004) Gender and other factors associated with the nonmedical use of abusable prescription drugs. *Subst Use Misuse* 39: 1-23.
19. Tetrault JM, Desai RA, Becker WC, Fiellin DA, Concato J, et al. (2008) Gender and non-medical use of prescription opioids: results from a national US survey. *Addiction* 103: 258-68.
20. Collier JD, Kroutil LA, Dai LA, Joseph C, Lanting GF, et al. (2006) Misuse of prescription drugs: data from the 2002, 2003, and 2004 National Surveys on Drug Use and Health. Substance Abuse and Mental Health Services Administration, Rockville, United States.
21. Kelly SM, Schwartz RP, O'Grady KE, Mitchell SG, Reisinger HS, et al. (2009) Gender differences among in- and out-of-treatment opioid-addicted individuals. *Am J Drug Alcohol Abuse* 35: 38–42.
22. Wagner FA, Anthony JC (2007) Male-female differences in the risk of progression from first use to dependence upon cannabis, cocaine, and alcohol. *Drug Alcohol Depend* 86: 191-8.
23. Hernandez-Avila CA, Rounsaville BJ, Kranzler HR (2004) Opioid-, cannabis-, and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol Depend* 74: 265-72.

24. Randall CL, Roberts JS, Del Boca FK, Carroll KM, Connors GJ, et al. (1999) Telescoping of landmark events associated with drinking: a gender comparison. *J Stud Alcohol* 60: 252-60.
25. Brady KT, Randall CL (1999) Gender differences in substance use disorders. *Psychiatr Clin North Am* 22: 241- 52.
26. Brady KT, Back SE, Greenfield SF (2009) *Women & addiction*. Guilford Press New York, United States
27. Sinha R (2001) How does stress increase risk of drug abuse and relapse? *Psychopharmacology* 142: 343-51.
28. Conway KP, Compton W, Stinson FS, Grant BF (2006) Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 67: 247-57.
29. Smith WB, Weisner C (2001) Women and alcohol problems: a critical analysis of the literature and unanswered questions. *Alcohol Clin Exp Res* 24: 1320-1.
30. Connors GJ, Maisto SA, Zywiak WH (1998) Male and female alcoholics' attributions regarding the onset and termination of relapses and the maintenance of abstinence. *J Subst Abuse* 10: 27-42.
31. Greenfield SF, Brooks AJ, Gordon SM, Green CA, Kropp F, et al. (2007) Substance abuse treatment entry, retention, and outcome in women: a review of the literature. *Drug Alcohol Depend* 86: 1-21.
32. Greenfield SF, Trucco EM, McHugh RK, Lincoln M, Gallop RJ (2007) The Women's Recovery Group Study: a stage I trial of women-focused group therapy for substance use disorders versus mixed-gender group drug counseling. *Drug Alcohol Depend* 90: 39-47.
33. Westermeyer J, Boedicker AE (2000) Course, severity, and treatment of substance abuse among women versus men. *Am J Drug Alcohol Abuse* 26: 523-35.
34. Najavits LM, Rosier M, Nolan AL, Freeman MC (2007) A new gender-based model for women's recovery from substance abuse: results of a pilot outcome study. *Am J Drug Alcohol Abuse* 33: 5-11.
35. Jones HE, Fitzgerald H, Johnson RE (2005) Males and females differ in response to opioid agonist medications. *Am J Addict* 14: 223-33.
36. Pettinati HM, Dundon W, Lipkin C (2004) Gender differences in response to sertraline pharmacotherapy in type A alcohol dependence. *Am J Addict* 13: 236-47.
37. Sadock BJ, Sadock VA (2007) *Kaplan & Sadock's synopsis of psychiatry: behavioural sciences/clinical psychiatry* (10th ed) Lippincott Williams & Wilkins, Philadelphia, United States.
38. Reinhertz HZ, Giaconia RM, Silverman AB, Friedman A, Pakiz B, et al. (1995) Early psychosocial risks for adolescent suicidal ideation and attempts. *J Am Acad Child Adolesc Psychiatry* 34: 599-611.
39. Sinha R, Fox H, Hong KI, Sofuoglu M, Morgan PT, et al. (2007) Sex steroid hormones, stress response, and drug craving in cocaine-dependent women: implications for relapse susceptibility. *Exp Clin Psychopharmacol* 15: 445-52.
40. Back SE, Waldrop AE, Saladin ME, Yeatts SD, Simpson A, et al. (2008) Effects of gender and cigarette smoking on reactivity to psychological and pharmacological stress provocation. *Psychoneuroendocrinology* 33: 560-8
41. Fox HC, Hong KA, Paliwal P, Morgan PT, Sinha R (2008) Altered levels of sex and stress steroid hormones assessed daily over a 28-day cycle in early abstinent cocaine-dependent females. *Psychopharmacology* 95: 527-36.
42. Griffin ML, Mendelson JH, Mello NK, Lex BW (1986) Marijuana use across the menstrual cycle. *Drug Alcohol Depend* 18: 213-24.
43. Lex BW, Mendelson JH, Bavli S, Harvey K, Mello NK (1984) Effects of acute marijuana smoking on pulse rate and mood states in women. *Psychopharmacology* 84: 178-87.
44. Turner JM, de Wit H (2006) Menstrual cycle phase and responses to drugs of abuse in humans. *Drug Alcohol Depend* 84:1-13.
45. Pope HG Jr, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D (2001) Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry* 58: 909-15.
46. Pope HG Jr, Jacobs A, Miallet JP, Yurgelun-Todd D, Gruber S (1997) Evidence for a sex-specific residual effect of cannabis on visuospatial memory. *Psychother Psychosom* 66: 179-84.
47. Goldstein RB (2009) Comorbidity of substance use with independent mood and anxiety disorders in women: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Women and addiction: a comprehensive handbook*. Guilford Press, New York, United States.
48. Greenfield, SF (2003) *Assessment of mood and substance use disorders. Integrated treatment for mood and substance use disorders*. Johns Hopkins University Press, Baltimore, United States.
49. Dahlgren L, Willander A (1989) Are special treatment facilities for female alcoholics needed? A controlled 2-year follow-up study from a specialized female unit (EWA) versus a mixed male/ female treatment facility. *Alcohol Clin Exp Res* 13: 499-504.
50. Ashley OS, Marsden ME, Brady TM (2003) Effectiveness of substance abuse treatment programming for women: a review. *Am J Drug Alcohol Abuse* 29: 19-53.