Research Article

iMedPub Journals
http://journals.imedpub.com

Journal of HIV & Retro Virus
ISSN 2471-9676

2017
Vol. 3 No. 1: 2

DOI: 10.21767/2471-9676.100029

HIV, Alcohol Use Disorders and Pain: New Findings to Address the Problem

Miguez-Burbano MJ[1], Espinoza L[2], Perez C[1] and Bueno D[1]

1 Florida International University, School of Integrated Sciences and Humanity, Miami, FL, USA
2 University of Miami Miller School of Medicine, Miami, FL, USA

Corresponding author:
Miguez-Burbano MJ

mjmiguez@fiu.edu

Florida International University, School of Integrated Sciences and Humanity Miami, FL, USA.

Tel: 7864273054

Citation: Miguez-Burbano MJ, Espinoza L, Perez C, et al. HIV, Alcohol Use Disorders and Pain: New Findings to Address the Problem. J HIV Retrovirus. 2017, 3:1.

Abstract

Background: Alcohol use and pain are frequent problems among people living with HIV/AIDS (PLWHA). Therefore, increasing the understanding of the interaction between these medical conditions is critical to improve health care and quality of life for this population. While gender differences in alcohol use and mood disorders are widely recognized, little is known about gender disparities in prescription of painkillers and correlates. Equally important is the lack of information regarding the role of neurotrophic factors although animal models have demonstrated BDNF pronociceptive effects.

Methods: Using a clinic-based sample of people living with H.I.V/AIDS (PLWHA), we investigated the prevalence and correlates associations of recent pain killer use. We also assessed the effects of gender, mood and Brain Derived Neurotrophic Factor levels (BDNF). Participants were 400 people living with HIV (PLWHA) who participated in the PADS cohort study.

Results: Approximately, a quarter (24%) of the sample reported regularly taking painkillers, and a correlation was evident with both CD4s and viral loads. Painkiller users were typically over 40. If they were males, painkiller users were more likely to be Caucasian; however, painkiller female users were more likely to be minorities. Factors related to painkiller use also differed between men and women. Analyses demonstrated that the weekly consumption of alcohol was significantly higher in the painkiller group compared to controls (19.4 ± 3.9 vs. 15.9 ± 1.34 drinks/week; p=0.03). Compared to non-hazardous alcohol users (non-HAU), female-hazardous alcohol users (HAU's) were more likely to be using prescription opioids (Odds Ratio: 4.6 95% Confidence Interval: 1-22.9, p=0.04). No such trend was observed among males. Noteworthy, higher scores of both depression and stress were observed among painkiller users. Gender differences were notable; women using painkillers exhibited significantly higher scores on both depression (19.6 ± 12.4 vs. 13.6 ± 11.7 total score; p=0.01), and stress (19.4 ± 8.3 vs. 14.9 ± 8.1 total score; p=0.004) while men did not. In our analyses, BDNF levels were significantly higher among subjects taking painkillers than those not taking them. In Longitudinal analyses, confirmed that hazardous alcohol use, BDNF levels, and gender were associated with greater odds of using painkillers at 6 months.

Conclusion: These findings highlight the importance of designing gender-sensitive surveillance, prevention, and treatment. Our findings extend earlier research by revealing that BDNF may account for important aspects of pain and alcohol abuse. The apparent implication of these findings is that interventions targeting BDNF may have considerable therapeutic potential in this population.

Keywords: Alcohol use; HIV/AIDS; Painkillers

Received: December 19, 2016; **Accepted:** February 23, 2017; **Published:** February 28, 2017

© Under License of Creative Commons Attribution 3.0 License | This article is available in: http://hiv.imedpub.com

Introduction

Chronic pain, defined as ongoing pain lasting longer than 6 months, is a significant problem among people living with HIV (PLWHA) [1]. Indeed, data suggests that as many two thirds of PLWHA reported suffering chronic pain [1]. Among PLWHA, pain may arise due to the direct effects of the virus on the central or peripheral nervous system. Notably, a sizable proportion of pain studies have been performed in the beginning of the epidemic, and pain was mostly associated with advanced stages of HIV/AIDS [2,3]. However, now-a-days the opposite side of the spectrum is also observed. With the widespread use of antiretrovirals, pain can emerge as the result of the toxic effects of certain treatment regimens. Dideoxynucleoside analogs inhibit neurite outgrowth. Nucleoside reverse transcriptase inhibitors also induce mitochondrial toxicity, triggering pain. Although less frequent, protease inhibitors have also been associated with pain [4].

Beyond direct tissue damage, chronic pain could be the result of central sensitization, in which the brain receives a strong signal of pain elicited by low or innocuous sensations [5]. Central sensitization has been associated with conditions such as addiction and neuropsychological disorders [5]. Central sensitization is particularly important in this group because a significant proportion of PLWHA abuse alcohol. Unfortunately, research in this area is still limited and highly debated [5-8], as it is unclear if: a) pain becomes a problem because pain thresholds are lowered in alcohol users when they are sober, or b) if these individuals are using increased amounts of alcohol looking for ethanol's potential analgesic effects or c) if pain is related to the subject's expectancies or mood.

Furthermore, pain research is largely limited to animal models or to studies of induced pain in laboratory settings where the emotional components and environmental stressors are not present. This is a significant drawback, as prior research has shown that mood and psychological distress are significant predictors of pain and painkiller use/abuse [9,10]. Accordingly, our multidimensional model includes biological, psychological and social variables. Our proposed model goes one step forward by proposing that a BDNF imbalance is an important biological mechanism mediating the increased rates of pain/pain killer use in PLWHA, particularly those using alcohol. This proposal is based on prior preclinical data indicating that pain sensitization is a form of maladaptive neuroplasticity, which is largely controlled by BDNF [11]. Studies to determine the relationship between pain, alcohol and BDNF among PLWHA are lacking, yet crucial first steps to improve knowledge and clinical management of pain. Therefore, this is the main goal of this article. If our postulates are correct, BDNF may represent a new target for drug development for this at need population.

Methods

Study population

The PADs (Platelet Alcohol Disorders Study 2010-2013) consists of 400 PLWHA who are at least 18 years old and under regular care at Miami's primary open-access public health system. Our choice of PLWHA in an open-access public health system with standard treatment protocols minimizes social, medical, and treatment inequalities that can confound our outcomes.

Non-ambulatory patients and those with major comorbidities (nervous system opportunistic infection, head injury, tumors, developmental disorders, severe malnutrition, or confirmed cardiovascular/immune diseases). To assure compliance and safety, individuals with major psychiatric disease (schizophrenia, bi-polar and maniac disorders) were also deemed ineligible.

To reduce the confounding effects of liver disease and/or illegal drug use, we also excluded injection and dependent drug users and any participants who had cirrhosis, active viral hepatitis or liver enzymes two standard deviations above normal values.

The protocol was approved by the Institutional Review Boards at Florida International University and the University of Miami. The study was conducted according to the principles expressed in the Declaration of Helsinki. Those participants who provided written informed consent and that signed a medical release form, were consequently enrolled and were followed over a period of six months.

Medical and pharmacologic history

Upon entry, medical history, including HIV and non-HIV related diseases, were obtained using structured questionnaires. The participant was asked to report any prescribed medication, and the interviewer documented names and doses. Our dependent variables of interest concern chronic pain that led to use of painkillers during the past six months. The survey specifically enquired about prescription of analgesics such as aspirin, acetaminophen, anti-inflammatory drugs and narcotic-like pain medications. Participants were provided with a list of the prescription drug classes noted above, to which they responded either "Yes" or "No" to each question. A similar procedure was used to document use of antiretroviral and antidepressant medications.

Alcohol drinking

At each visit, using a non-judgmental interview style (questions are delivered using neutral wording), participants were asked about alcohol intakes in the past six months, using the Alcohol Use Disorders Identification Test (AUDIT) and the Alcohol Dependence Scale (ADS) [11,12]. Participants were asked to report a serving size using models of 12 ounces of beer, 5 ounces of wine or 1.5 ounces of liquor. Alcohol consumption scores were computed by averaging cross products of quantity and frequency of beer/wine and hard liquor. Then, based on the National Institute of Alcohol Abuse and Alcoholism criteria, the sample was dichotomized in two groups: hazardous (men who reported >14 drinks/week or >4 drinks in one day, and women who reported >7 drinks/week or >3 drinks in one day) or non-hazardous alcohol users, for those who reported fewer drinks [13]. Participants who drank more than five standard drinks in a given day were considered binge drinkers [13].

Depression

A trained assessor completed the Beck Depression Inventory II (BDI-II) questionnaire. The BDI is one of the most widely used instruments to screen and to measure the intensity of depression [14]. A total score of 0–9 is considered to be normal, 10-18 corresponds to mildly depressed, 19-28 equals moderate depression, and scores above 29 are considered severe depression [14].

Perceived stress scale (PSS)

Developed by Cohen and colleagues, the Perceived Stress Scale (PSS) is a widely used scale to measure stress in chronic conditions, and therefore we deemed it appropriate to use on PLWHA. Participants responded to 10 questions, to assess whether they perceive their lives as unpredictable, uncontrollable or overloaded [15]. The PSS is not a diagnostic test and therefore there are no cut-offs to determine stressed individuals. Accordingly, stress levels were analyzed by quartiles [15]. Each of the four groupings of stress levels was analyzed for significant associations with our dependent variables.

Brain derived neurotrophic factor

Circulating levels of BDNF were selected in this study because prior studies had demonstrated that, although different from those in the cerebrospinal fluid (CSF), they correlate with CSF measures in other CNS diseases [16]. To obtain platelet-poor plasma, blood samples were collected in EDTA-coated tubes (plasma) (BD Diagnostic Systems, NJ, USA), and were stored on ice. Plasma was separated by centrifugation at 40ºC for 15 min at 1,500x g. This plasma was again re-centrifuged at 10,000x g and stored in polypropylene tubes at -80ºC until assayed. BDNF levels were measured using a commercially available ELISA kit (R&D System), according to the manufacturer's instructions. The repeatability of the BDNF ELISA, as measured by intra-assay precision, was 6%, and the reproducibility as measured by inter-assay precision was 9%. Coefficient of variation was 7.9 (CV%=SD/mean × 100%).

Potential confounders

A number of plausible confounders were measured, and included age, sex, race/ethnicity and years of education (1=less than high school; 2=high school graduate; 3=some college; 4=college graduate or more). Socioeconomic status was assessed as follows: 1=$0–10,000; 2=$10,000–$25,000; 3=$25,000-50,000 and 4=>$50,000 (range: 0–$75,001+). Overall, nutritional status was determined by measurements of serum albumin levels. In addition, the following HIV associated variables were assessed: time since diagnosis, time receiving antiretroviral therapy, HIV-specific clinical history, CD4's and Viral load (AMPLICOR HIV-1 monitor test, Roche Diagnostics, Branchburg, NJ).

Statistical analyses

The normality of the distribution of primary outcomes of interest was examined with a normal probability plot. Descriptive statistics (minimum, maximum, median and mean with standard deviation) were used to summarize the data. Group comparisons were assessed using the chi-square test for categorical variables, two sample Student's t-test for normally distributed continuous variables, and the Wilcoxon rank sum test for non-parametrically distributed continuous variables. We employed the Bonferroni correction, because of the multiple comparisons. Alcohol use variables BDNF, BDI, STAI and PSS scores were assessed as continuous and categorical variables.

Univariate and bivariate associations between independent variables and past-year use of painkiller were reported as unadjusted odds ratios (OR) and 95% confidence intervals (CI). Statistical significance was assessed at $\alpha = 0.05$. To examine potential mediators of painkiller use, regression models were employed. The validity of model assumptions was evaluated using analysis of residuals. Two-tailed P values less than 0.05 were considered significant. To examine predictors of painkiller use logistic regression analyses were conducted. Variables that were non-significant were removed from the model one at a time. Data analyses were performed using SPSS version 20.

Results

Sociodemographics

Since understanding the characteristics (i.e., demographic, socioeconomic) of painkiller users is important for properly tailoring interventions we start with these analyses. **Table 1** highlights the sociodemographic similarities and differences between those receiving painkillers and their counterparts. A higher proportion of women than men were taking these medications. There were also gender disparities as more men endorsed using both painkillers and antidepressants (10% versus 3%, p=0.05) but not women (5% vs. 3%).

Table 1 Sociodemographic and clinical characteristics of HIV infected patients by BMI.

Variable	Painkillers (n=52)	Non-Pain Killers (n=348)	P value
Age	44.5 ± 5.1	42.3 ± 6.5	0.7
Men	14%	86%	0.05
Women	22%	78%	
African American	14%	86%	0.2
Hispanic	17%	83%	
White	20%	80%	
Annual Income:	85%	88%	0.7
Less than $10,000			
$11,000-$20,000	11%	8%	
$20,000-$49,000	2%	2%	
>$50,000	2%	2%	
Education (years of school)	12.1 ± 2.1	11.3 ± 2.4	0.1
Triglycerides	129.5 ± 56.4	140.3 ± 74.5	0.4
CD4 cell counts	556 ± 369	423.6 ± 276.9	0.02
Viral Load	13785 ± 7637	40766.0 ± 10293	0.04

Note: Demographic characteristics were expressed as percentages by BMI groups. Biological measures were presented as means and standard deviations

© Under License of Creative Commons Attribution 3.0 License

Regarding racial differences in painkiller use, rates were significantly higher among Caucasians, with the lowest rates reported by African Americans. However, additional analyses indicated that higher rates of painkiller use among Caucasians were limited to males. Among them, 40% of Caucasians but only 16% of Hispanics used painkillers. Among females, the highest rates of painkiller use occurred among Hispanics (39%), followed by African Americans (29%), and lastly Caucasian females (21%). Notably, the painkiller group was slightly more educated (>high school level).

Prescribed medications

Almost all study participants were receiving anti-retroviral therapy. Most were receiving Truvada: 44%, Atripla: 22%, alone or in combination with Norvir: 32% or Kaletra: 13%. Adherence, as measured by the ACTG questionnaire, was similar between the groups, and was high during the week (93%), and is more limited during weekends (83%).

Approximately a quarter of the sample was taking painkillers on a regular basis and was defined as our painkiller group; the remaining subjects were included as controls for the analyses. A quarter of the population was taking narcotic-like painkillers. Non-steroidal anti-inflammatory drugs (NSAIDs) and hydrocodone/acetaminophen were the most frequently prescribed medications. Near a third was using hydrocodone/acetaminophen. Half were taking high doses of ibuprofen (800-1200 mg). Eight percent of the population receiving painkillers was also prescribed antidepressants, which contrasts with only 5% among the control group. Consistent with either chronic pain or an addiction model, these rates did not vary during the 6 month period of this analysis.

Painkillers and BDNF

Use of painkillers was significantly associated with levels of BDNF (r=–0.154, p=0.003). Notably, BDNF levels were higher in subjects receiving opioid-painkiller as compared to controls (11983 ± 9502 versus 7429 6035 pg/ml, p=0.04). No such relationship was observed when comparing individuals taking non-steroidal anti-inflammatory drugs with controls, suggesting that BDNF responds completely differently with opioid administration compared to other types of painkillers.

Painkillers and HIV disease

Despite no differences in treatment or adherence, we proceeded to assess the relationship between painkillers and antiretroviral therapy. A significant correlation was found between painkillers and CD4 cell counts (r=0.134, p=0.009). At baseline, those receiving painkillers exhibited significantly higher CD4 counts (556.1 ± 368 cells/mm^3) than those without them (423.1 ± 276.9 cells/mm^3, p=0.0001). Significant group differences in viral loads were also observed; the painkiller users exhibited lower viral loads (13785 ± 7637 versus 40766 ± 10293 copies/mL, p=0.04). However, results were only significant among those not using opioid medications.

Painkillers and alcohol

Since alcohol use may interact with the experience of pain in a number of ways, we explored their relationship. After controlling for various factors, analyses indicated significant correlations between painkiller use and number of days per week drinking (r=0.183, p=0.000), and total number of drinks consumed per week (r=0.132, p=0.009). Indeed, the painkiller group drank on average 3 days per week versus two days in the comparison group (P=0.02). They also drank approximately one additional drink per occasion (4.7 ± 0.9 vs. 4.0 ± 0.26; P=0.09). This resulted in a significantly higher consumption per week among those in the painkiller group (19.4 ± 3.9 vs. 15.9 ± 1.34 drinks/week; p=0.03).

Since the literature surrounding gender and alcohol abuse indicates important gender differences, we pursued such analyses. HAU men exhibited a moderate risk of using painkillers (OR: 1.66 95% CI: 0.8-3.2, p=0.09). Notably, HAU women were significantly more likely than men to hoard painkiller medications (OR: 4.6 95% CI: 2.1-10.2, p=0.0001). Additional analyses indicated that HAU females were more likely to be taking prescription opioids than non-HAU females (OR: 4.6 95% CI: 1-22.9, p=0.04). No such trend was observed among males.

Painkiller use and mood disorders

Since some individuals may misuse painkillers for their anxiolytic and possible antidepressant properties, we explored the possible relationship. Notably, the association between PK users and mood disorders differed by gender. Male painkiller users exhibited significantly higher stress scores than non- painkiller users (18.2 ± 8.0 vs. 15.1 ± 9.2; p=0.03). However, they did not differ on depression scores (PK: 17.7 ± 12.2 vs. 16.5 ± 12.1; p=0.4). Meanwhile, women using painkillers exhibited significantly higher scores on both depression (19.6 ± 12.4 vs. 13.6 ± 11.7; p=0.01) and stress (19.4 ± 8.3 vs. 14.9 ± 8.1; p=0.004) than the corresponding female counterparts.

Final model

Multivariate analyses revealed that painkiller use at the last visit was predicted by hazardous alcohol use, BDNF levels and gender after controlling for sociodemographic factors, antiretroviral treatment and baseline HIV disease status. As depicted in **Table 2**, the last variables to be eliminated were age, education and viral load.

Discussion

Consistent with prior research, our data indicated rates of pain killer use of 25%, which was constant over the 6-month follow-ups of the study. These rates are higher than those reported for the general population (14%). Although rates were high across the board, we found a higher prevalence of painkiller use among women [17,18]. Gender comparisons of painkiller-correlates also revealed marked differences. While rates of painkillers use among men were higher among Caucasians than among minorities, quite the opposite occurred among women.

Table 2 Multivariate analyses.

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Alcohol Users	0.171	0.043	0.202	4.008	0	0.087	0.255
BDNF	–8.28E-06	0	–0.13	–2.518	0.012	0	0
Gender	–0.099	0.046	–0.112	–2.165	0.031	–0.19	–0.009
Education	–0.016	0.009	–0.087	–1.715	0.087	–0.034	0.002
Age	–0.006	0.003	–0.088	–1.748	0.081	–0.012	0.001
Viral Load	9.94E-08	0	0.043	0.839	0.402	0	0

Additional analyses discovered increased rates of painkiller use among female hazardous alcohol users. The data suggests that prevention and treatment efforts for this population are likely to require some tailoring. This is especially true for hazardous alcohol users who may have different needs than other segments of the population because of associated comorbid conditions. Findings are highly significant, as they fill important knowledge gaps in the literature by examining gender differences and contrasting factors associated with use of painkillers.

Equally important was the discovery that BDNF, which is particularly altered among alcohol users living with HIV, was a significant predictor of using painkillers. Results are probably related to the neurotoxic effects of alcohol that may trigger BDNF as a compensatory mechanism. Yet it is also possible, based in recent evidence, that BDNF is involved in the neuronal mechanism underlying pain development and transmission [19]. BDNF may enact by altering neuronal sensitivity to painful stimuli. It may also modify the expression of thermo-transient receptor potential (thermo-TRP) channels. As such, BDNF manipulations have been attempted in animals to modify pain with success and thus it could be in the future incorporated in the pain-medicine armamentarium.

In the past pain was associated with advanced HIV disease [2,3,20], but our cohort analyses indicated that subjects with high CD4 counts and lower viral loads more frequently used painkillers. Based on these findings one can posit that PLWHA receiving antiretroviral therapy may be at a higher risk of developing neuropathies leading to increased painkiller use [4]. However, it's possible that anti-inflammatory painkillers, by reducing the inflammatory response, are thereby improving viral control and cellular immune responses. It is also important to highlight that opioids, which are known to be immunosuppressives, did not show these benefits.

If prior estimates of pain in PLWHA (30-80%) are correct [3], then our findings that only 24% are receiving painkillers suggests that these individuals are under-treated. The under-treatment of pain results in needless suffering, and reduces quality of life. But most importantly, it may lead to inappropriate use of alcohol for pain relief, resulting in a vicious cycle that will be harder to interrupt.

Although the effects of alcohol and pain have been extensively studied in animal models and in the general population, the literature is extremely scarce in the HIV infected population. Our findings that HAU are more likely to be using pain medications are of great concern. Accordingly, interventionists need to recognize that during the phase of alcohol withdrawal subjects may develop hyperalgesia [21]. Another important issue to be considered is whether or not hazardous alcohol users' needs lower or higher doses of pain medications. Unfortunately, the literature is not only limited, it is also conflicting. While the natural tendency will be to reduce the doses, experts like Perry argued that they should receive more pain medication, not less, in order to compensate for their developed tolerance [22] yet, because of the heightened risk of transitioning to non-medical use, additional studies are urgently needed. It is essential to have a clear protocol to follow when providers are confronted with subjects with multiple comorbidities. These findings indicate the need for prevention and intervention efforts tailored to this population with multiple comorbidities.

Conclusion

The management of chronic pain is a complex one, because individuals suffering from chronic pain frequently have other concomitant medical and psychiatric conditions, including mood disorders. While use of painkillers may be less influenced by depression for men than for women, it appears that psychological distress is highly influential in both. It is well documented that women in the general population and PLWHA evidence higher rates of mood disorders (e.g. depression, anxiety) [23]. Concurrent conditions among women need to be assessed and addressed in treatments, as they may be etiologically related. Findings are in line with our prior studies indicating that distress is an important trigger for BDNF alterations, as well as for alcohol use. Irrespective of gender, clinical interventions, and pharmacologic treatments aimed at targeting and mitigating psychological distress may serve as an important preventative function. Irrespective of gender, interventions addressing psychological distress may mitigate some of these relevant clinical issues.

Beyond these important demographic factors, race and gender remain as key factors in patterns of alcohol use behaviors, yet they remain understudied aspects of pain and pain killer use [24]. Similar to our findings, studies among the general population show that Caucasians tend to use painkillers at higher rates than minority groups [25-27]. Yet, among females we have discovered that Hispanics and African American women are more likely to use painkillers. This pattern deserves further investigation.

© Under License of Creative Commons Attribution 3.0 License

References

1 Dobalian A, Tsao JC, Duncan RP (2004) Pain and the use of outpatient services among persons with HIV: Results from a nationally representative survey. Med Care 42: 129-38.

2 Nair SN, Mary TR, Prarthana S, Harrison P (2009) Prevalence of pain in patients with HIV/AIDS: A cross-sectional survey in a South Indian State. Indian J Palliat Care, 15: 67–70.

3 Aouizerat BE, Miaskowski CA, Gay C, Portillo CJ, Coggins T, et al. (2010) Risk factors and symptoms associated with pain in HIV-infected adults. JANAC 21: 125-33.

4 Montessori V, Press N, Harris M, Akagi L, Montaner JS (2004) Adverse effects of antiretroviral therapy for HIV infection. CMAJ 170: 229-238.

5 Apkarian AV, Neugebauer V, Koob G, Edwards S, Levine JD, et al. (2013) Neural mechanisms of pain and alcohol dependence. Pharmacol Biochem Behav 112: 34–41.

6 Tsao JC, Dobalian A, Naliboff BD (2004) Panic disorder and pain in a national sample of persons living with HIV. Pain 109: 172-180.

7 Merlin JS, Westfall AO, Raper JL, Zinski A, Norton WE, et al. (2012) Pain, mood and substance abuse in HIV: Implications for clinic visit utilization, antiretroviral therapy adherence and virologic failure. J Acquir Immune Defic Syndr 61: 164.

8 Askay SW, Bombardier CH, Patterson DR (2009) Effect of acute and chronic alcohol abuse on pain management in a trauma center. Expert Rev Neurother 9: 271-277.

9 Martins SS, Fenton MC, Keyes KM, Blanco C, Zhu H, et al. (2012). Mood/anxiety disorders and their association with non-medical prescription opioid use and prescription opioid use disorder: Longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. Psychol Med 42: 1261–1272.

10 Carleton RN, Abrams MP, Asmundson GJ, Antony MM, McCabe RE (2009) Pain-related anxiety and anxiety sensitivity across anxiety and depressive disorders. J Anxiety Disord 23: 791-798.

11 Garraway SM, Huie JR (2016) Spinal plasticity and behavior: BDNF-induced neuromodulation in uninjured and injured spinal cord. Neural Plast.

12 Piccinelli M (1998) Alcohol use disorders identification test (AUDIT). Epidemiol Psichiatr Soc 7: 70-73.

13 Skinner HA, Horn JL (1984) Alcohol dependence scale (ADS) user's guide. Addiction Research Foundation 1984.

14 National Institutes of Health (2015) Drinking levels defined. National Institute on Alcohol Abuse and Alcoholism (NIAAA).

15 Beck AT, Steer RA, Brown GK (1996) Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation.

16 Cohen S, Kamarck T, Mermelstein R (1983) A global measure of perceived stress. J Health Soc Behav, pp: 385-396.

17 Pillai A, Kale A, Joshi S, Naphade N, Raju MS, et al. (2010) Decreased BDNF levels in CSF of drug-naive first-episode psychotic subjects: correlation with plasma BDNF and psychopathology. Int J Neuropsychopharmacol 13: 535–539.

18 http://www.npr.org/sections/health-shots/2014/07/01/327308769/state-of-the-painkiller-nation-wide-variation-in-prescription-rates

19 Greenfield SF, Back SE, Lawson K, Brady KT (2010) Substance abuse in women. Psychiatr Clin North Am 33: 339-355.

20 Siniscalco D, Giordano C, Rossi F, Maione S, de Novellis V (2011) Role of Neurotrophins in Neuropathic Pain. Curr Neuropharmacol 9: 523–529.

21 Dobalian A, Tsao JC, Duncan RP (2004) Pain and the use of outpatient services among persons with HIV: Results from a nationally representative survey. Med Care 42: 129-138.

22 Dina OA, Messing RO, Levine JD. Ethanol withdrawal induces hyperalgesia mediated by PKCepsilon. Eur J Neurosci 24: 197-204

23 Perry BA, Westfall AO, Molony E, Tucker R, Ritchie C, et al. (2013) Characteristics of an ambulatory palliative care clinic for HIV-infected patients. J Palliat Med 16: 934-937.

24 Brady C, Mousa SS, Mousa SA (2009) Polycystic ovary syndrome and its impact on women's quality of life: More than just an endocrine disorder. Drug Healthc Patient Saf 1: 9-15.

25 Grov C, Bimbi DS, NaníN JE, Parsons JT (2006) Race, ethnicity, gender and generational factors associated with the coming-out process among gay, lesbian and bisexual individuals. J Sex Res 43: 115-121.

26 Bachman JG, Wallace Jr JM, O'Malley PM, Johnston LD, Kurth CL, et al. (1991) Racial/ethnic differences in smoking, drinking, and illicit drug use among American high school seniors, 1976-1989. Am J Public Health 81: 372-377.

27 Wallace JM, Bachman JG, O'Malley PM, Schulenberg JE, Cooper SM, et al. (2003) Gender and ethnic differences in smoking, drinking and illicit drug use among American 8th, 10th and 12th grade students, 1976–2000. Addiction 98: 225-234.