International Journal of Risk & Safety in Medicine 25 (2013) 105–109
DOI 10.3233/JRS-130586
IOS Press

Case Report

New onset alcohol dependence linked to treatment with selective serotonin reuptake inhibitors

Onome V. Atigari, Anne-Marie Kelly, Qamar Jabeen and David Healy*
Department of Psychological Medicine, Hergest Unit, Ysbyty Gwynedd Hospital, Wales, UK

Received 16 December 2012
Accepted 7 January 2013

Abstract.
BACKGROUND: Genetic and environmental factors influence the development of alcohol dependence and alcohol dependence increases the risk of developing Major Depressive Disorder-MDD (vice versa). Amongst antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are likely the most frequently prescribed for MDD. However, findings on the role of SSRIs in alleviating alcoholism are conflicting.
CASE DESCRIPTION: A review of the literature is highlighted with a case of middle-aged lady with new onset alcohol dependence syndrome after commencement of SSRI, which resolved following discontinuation of the SSRIs and the introduction of Mirtazapine.
DISCUSSION: The serotonin transporter gene has been linked to excessive drinking, early-onset problem drinking, alcohol dependence, anxiety and impulsiveness. While the evidence for antidepressant use appears consistent in alleviating depressive symptoms in patients with comorbid alcohol dependence and depression, some groups of patients may show an increase in alcohol consumption. Alternatively, there are a series of studies suggesting that antagonism of S-3 receptors can lead to diminished cravings for alcohol. This case highlights the need for further research into the effects of SSRIs on alcohol consumption in those with and without previous alcohol dependence syndromes. It also indicates a need to monitor changes in alcohol consumption and behaviour while on SSRIs.

Keywords: Alcohol, serotonin, depression, antidepressants

1. Introduction

Alcohol dependence increases the risk of developing Major Depressive Disorder (MDD) and vice versa [1, 2]. Amongst people with a current diagnosis of alcohol dependence the prevalence rate of an independent major depressive disorder is 20.5% [1]. The features of both conditions overlap to some extent and the outcome of each disorder is thought to be worse in the presence of the other [3].

The annual cost of alcohol misuse is increasing worldwide, with the estimated rise to the Health Service in the United Kingdom increasing from £1.7 to £2.7 Billion in 2006/2007 [4]. In the year 2010/11 alone, alcohol related hospital admissions increased to 1,168,300 in England [5]. Given the scale of MDD

*Address for correspondence: David Healy, Department of Psychological Medicine, Hergest Unit, Ysbyty Gwynedd Hospital, Wales, LL57 2PW, UK. Tel.: +44 1248384384; E-mail: David.Healy54@googlemail.com.

and Alcohol Use Disorders (AUD), it is essential to have an effective primary, secondary and tertiary prevention for AUD when managing patients with MDD and vice versa.

Management options for MDD include, but are not limited to the use of antidepressants. Amongst the antidepressants, the selective serotonin reuptake inhibitors (SSRIs) are likely the most frequently prescribed.

The exact cause for the development of an AUD is not known. However, the risks are multifactorial. Genetic factors are thought to play a role and a reduction in serotonergic transmission has been linked to increased alcohol intake and vice versa in both preclinical and clinical studies [6]. However, the evidence for modulating serotonergic transmission in an attempt to treat AUDs is conflicting.

This case which we report with informed consent outlines the development of an alcohol dependence syndrome after treatment for depression with the selective serotonin reuptake inhibitors paroxetine and citalopram.

2. Case report

Ms X was born in England. Her parents divorced when she was 6 years old. She and her twin brother lived with their father. Ms X described her father as kind and caring, but she had a difficult relationship with her step-mother. At the age of 16 yrs she attended Child Guidance for panic attacks. Despite this she studied up to GCSE level and subsequently worked as a Health Care Assistant for over 14 years, owning her own house and car.

At the age of 20 years, Ms X had a serious car accident. She subsequently developed panic attacks and anxiety while driving, but kept working.

Twelve years later, her father died suddenly from pneumonia. During the funeral she choked on a soft drink and became cyanosed, requiring assistance. A month after the funeral she developed a depressive disorder associated with a specific phobia of choking on food. Her food intake reduced. After getting worse over a year, she was put on sertraline and switched soon after to 20 mg of paroxetine which she remained on for 6 years. While slow to respond to paroxetine initially, Ms X described an improvement in her mood, energy, motivation and confidence. There was also relief of her choking phobia and anxieties about driving.

Prior to paroxetine, Ms X was a social drinker, with an alcohol intake within the normal limit and she has no family history of AUDs. She had no medical history of note. Apart from the recent loss of her father, there were no other identifiable psychosocial stressors. She was high functioning at work and maintained stable interpersonal relationships. The labelling of paroxetine does not preclude social drinking. But following resolution of her symptoms and within months of being on paroxetine, Ms X developed new onset and increasing cravings for alcohol. She found her drinking escalated from a few glasses to an average of 6 to 8 bottles of wine (alcohol 13% volume) weekly. She was diagnosed as alcohol dependent.

Ms X began saying and doing things of which she had no memory afterwards. She was banned from restaurants and bars and close friends and family distanced themselves from her. She noted the changes, but was unconcerned. Her behavior became verbally aggressive and reckless. She engaged in risky behaviors such as climbing out of a velux window onto the roof, apparently unconcerned about the dangers of what she was doing. Ms X began to make continual phone calls to the police station when she was drinking, sometimes 20 to 30 times a night on their non-emergency number. She claims only a vague memory of doing so. However, this resulted in her arrest on several occasions. On one occasion, she assaulted a police officer.

There was lack of ability to control alcohol use. She would start drinking and not stop until she was arrested or collapsed into a coma. Her medical records at this time show diagnoses of exaggerated alcohol intoxication and pathological alcohol intoxication with an associated disinhibition. She was reported as being hyperactive, detached, overtalkative, impulsive and disinhibited. She noted that she would talk inappropriately to strangers. On three occasions she reversed her car into a tree, without concern. There were also reports of impairment in her memory and concentration.

Alcoholic fetor, frequent mistakes, time off work and concerns about her judgement led to the loss of her job. This change represented a significant shift from her premorbid personality and this finding was corroborated by others including her employers.

As a result of her multiple arrests, she developed an extensive forensic record. She was charged with nuisance offences. As a result of this she was medically assessed. The opinions put forward to explain the changes in her behaviour included an interaction between antidepressants and alcohol, and the development of a hypomania secondary to SSRI intake.

Already concerned that paroxetine had had a role in these changes she had requested a switch from paroxetine to another antidepressant and was put on citalopram 20 mg daily in 2005. In the same year she was referred to an alcohol service, where she was told that her perceptions that her SSRI might be causing her problem indicated the kind of denial that is typical of alcoholism. Several months' alcohol free while in rehabilitation did not interrupt the pattern. She remained on citalopram until 2009, and her alcohol cravings and consumption and problem behaviours persisted.

In 2010, at her request Ms X's antidepressant was changed to Mirtazapine. Since then her alcohol consumption has stopped entirely and her antisocial behaviours have also stopped. Her phobia of choking has reappeared but is mild.

3. Discussion

Both genetic and environmental factors influence the development of alcohol dependence. The genetic contribution is shown by twin adoption studies in which the variance in heritability attributable to genetic factors is 40% to 66% [7, 8]. To date associations have been found between alcohol dependence and the dopamine transporter gene [9], the monoamine oxidase A gene [10], the D2 dopamine receptor gene [11], and the serotonin transporter gene [12–14].

The serotonin transporter gene has been linked to excessive drinking, early-onset problem drinking, alcohol dependence, anxiety and impulsiveness [14, 15]. A variety of explanations have been put forward for this link, including a reduced serotonin availability in the brain leading to alcohol-seeking behaviour [6]. Polymorphism at the promoter region of serotonin transporter gene (5-HTTLPR) influences the function of the 5-HTT [12]; and several studies have implicated the 5-HTTLPR short allele with increase in alcohol consumption [12, 16].

Given suggestions of serotonergic dysfunction in alcohol dependence, several studies have been conducted into the role of SSRIs in alleviating alcoholism. The findings are conflicting. While the evidence for antidepressant use in conjunction with psychosocial treatment is consistent in showing an alleviation of depressive symptoms in patients with comorbid alcohol dependence and depression, their impact on reducing alcohol use was found to be minimal [13].

Laboratory studies pointing to differences in serotonergic functioning from one alcoholic subtype to another have raised the possibility of a differential impact of SSRI on alcoholic subtypes [15, 17]. While some clinical studies show a beneficial effect of SSRIs on alcohol consumption in heavy drinkers, others

show an increase in alcohol consumption particularly in early onset drinker [18]. There is a developing consensus that SSRIs have minimal beneficial impact or can exacerbate alcohol use in early-onset, higher severity and higher risk alcohol users [19–21]. This has led to recommendations that SSRIs be used cautiously or avoided in this group [19–21]. Also worthy of note in addition is the over 390 reports to the Food and Drug Administration (FDA) suggesting the development of an AUD while on either paroxetine or Citalopram [22].

In contrast, there are a series of studies suggesting that antagonism of S-3 receptors can lead to diminish cravings for alcohol [23] and gradually reduce consumption.

In the case of Ms X, using the Bradford Hill criteria for causation there are a number of factors that point to a link between her alcohol dependence and SSRI intake. First, there was a temporal relationship between starting an SSRI and development of alcohol cravings and subsequent alcohol dependence syndrome (ADS). Second while there were other stressors such as recent bereavement, choking phobia and depression which may have contributed to the development of her alcohol dependence, it is worth noting that she had a previous history of anxiety and panic attacks which did not precipitate alcohol dependence. It is also notable that her anxiety and depression had cleared before her alcohol dependence commenced.

Third, the switch in medication from SSRIs to the S-3 receptor antagonist, mirtazapine, resulted in a resolution of the alcoholic cravings and AUD. This demonstrates empirical support for a theoretical antidote. Fourth and fifth respectively is the evidence for biological plausibility and consistency cited above, as well as numerous case reports on the internet but not in the academic literature.

An alternate explanation of her alcohol abuse and disinhibited behaviour is that she developed hypomanic symptoms secondary to SSRI treatment. It should be noted that the presentation did not constitute bipolar affective disorder. The behavioural changes followed the diagnosis of ADS and occurred only in the context of alcohol and/ or SSRI use and have not reoccurred since the discontinuation of the SSRIs and resolution of the AUD.

This case highlights the need for further research into the effects of SSRIs on alcohol consumption in those with and without previous alcohol dependence syndromes. Despite the established efficacy of SSRIs in treating various disorders, and possible benefit in managing depressive symptoms linked to alcohol intake, there appears to be a need to monitor changes in alcohol consumption and behaviour while on SSRIs. In patients who develop a new-onset alcohol dependence syndrome while on SSRI, it is worth reviewing the SSRIs against the background of other biopsychosocial risk factors in the investigation of causality. Depending on an appraisal of benefits and risks it may be necessary in some cases to withhold or switch the SSRI as part of an appropriate management strategy.

Conflict of interest

None.

References

[1] Pettinati MH, Dundon WD. Comorbid depression and alcohol dependence new approaches to dual therapy challenges and progress. Psychiatric Times 2011;28(6):1.
[2] Boden JM, Fergusson DM. Alcohol and depression. Addiction 2011;106(5):906-14.
[3] Sullivan LE, Fiellin DA, O'connor PG. The prevalence and impact of alcohol problems in major depression: A systematic review. The American Journal of Medicine 2005;118(4):330-41.

[4] Health and Social Care Information Centre. Statistics on Alcohol: England, 2012. Cited 20.09.2012. http://www.ic.nhs.uk/webfiles/publications/003_Health_Lifestyles/Alcohol_2012/Statistics_on_Alcohol_England_2012.pdf
[5] Health and Social Care Information Centre. Statistics on Alcohol: England, 2012. Cited 20.09.2012. http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/alcohol/statistics-on-alcohol-england-2012-[ns]
[6] LeMarquand D, Pihl RO, Benkelfat C. Serotonin and alcohol intake, abuse and dependence: Clinical evidence. Biol Psychiatry 1994;36(5):326-37.
[7] Agrawal A, Verweij KJH, Gillespie NA, Heath AC, Lessov-Schlaggar CN, Martin NG, Nelson EC, Slutske WS, Whitfield JB, Lynskey MT. The genetics of addiction-a translational perspective. Transl Psychiatry 2012;2:e140. doi: 10.1038/tp.2012.54
[8] Lowinson JH, Ruiz P, Millman RB, Langrod JG. Substance Abuse A Comprehensive Textbook, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005;33-47.
[9] Köhnke MD, Batra A, Kolb W, Köhnke AM, Lutz U, Schick S, Gaertner I. Association of the dopamine transporter gene with alcoholism. Alcohol Alcohol 2005;40:339-42.
[10] Contini V, Marques FZC, Garcia CED, Hutz MH, Bau CHD. MAOA-uVNTR polymorphism in a Brazilian sample: Further support for the association with impulsive behaviors and alcohol dependence. Am J Med Genet B: Neuropsychiatr Genet 2006;141B:305-8.
[11] Smith L, Watson M, Gates S, Ball D, Foxcroft D. Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: A HuGE gene-disease association review. Am J Epidemiol 2008;167:125-38.
[12] McHugh RK, Hofmann SG, Asnaani A, Sawyer AT, Otto MW. The serotonin transporter gene and risk for alcohol dependence: A meta-analytic review. Drug and Alcohol Dependence 2010;108(1-2):1-6.
[13] Pettinati HM. Antidepressant treatment of co-occurring depression and alcohol dependence. Biological Psychiatry 2004;56(10):785-92.
[14] Choi I, Kee BS, Son H, Ham BJ, Yang BH, Kim SH, Lee J, Son BK, Lee B, Lee S, Chai Y, Shin HD. Genetic polymorphisms of alcohol and aldehyde dehydrogenase, dopamine and serotonin transporters in familial and non-familial alcoholism. European Neuropsychopharmacology 2006;16(2):123-8.
[15] Pettinati HM, Kranzler HR, Madaras J. The status of serotonin-selective pharmacotherapy in the treatment of alcohol dependence. Recent Dev Alcohol 2003;16:247-62.
[16] van der Zwaluw CS, Engels RC, Vermulst AA, Rose RJ, Verkes RJ, Buitelaar J, Franke B, Scholte RH. A serotonin transporter polymorphism (5-HTTLPR) predicts the development of adolescent alcohol use. Drug and Alcohol Dependence 2010;112(1-2):134-9.
[17] Fils-Aime ML, Eckardt MJ, George DT Brown GL, Mefford I, Linnoila M. Early-onset alcoholics have lower cerebrospinal fluid 5-hydroxyindoleacetic acid levels than late-onset alcoholics. Arch Gen Psychiatry 1996;53(3):211-6.
[18] Berggren U, Eriksson M, Fahlke C, Balldin J. Relationship between central serotonergic neurotransmission and reduction in alcohol intake by citalopram. Drug and Alcohol Dependence 2001;63(3):263-7.
[19] Kranzler HR, Burleson JA, Brown J, Babor TF. Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics. Alcoholism: Clinical and Experimental Research. Alcohol Clin Exp Res 1996;20(9):1534-41.
[20] Pettinati HM, Volpicelli JR, Kranzler HR, Luck G, Rukstalis MR, Cnaan A. Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. Alcoholism: Clinical and Experimental Research [0145-6008] 2000;24(7):1041-9.
[21] Australian Government National Drug Strategy. Comorbidity of mental disorders and substance use: A brief guide for the primary care clinician. Updated 2007-2008. Cited 19.10.2012 http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/publishing.nsf/Content/mono71-toc~mono71-5~mono71-5-4
[22] Rxisk.org FDA drug information. Cited 07.12.12 https://www.rxisk.org/Research/DrugInformation.aspx?nc=1354872628000&DrugID=4332&ProductDrugID=-5605&ProductName=Cipramil#8_0_0_0_0_–_alcohol
[23] Hodge CW, Kelley PS, Bratt AM, Iller K, Schroeder JP, Besheer J. 5-HT3A receptor subunit is required for 5-HT3 antagonist-induced reductions in alcohol drinking. Neuropsychopharmacology 2004;29:1807-13.

PHARMACOVIGILANCE EUROPE

	Yes	No
Ranbaxy	☒	☐
Serious	☒	☐
HCP	☒	☐

	ADR	PQC	ADR+PQC	MI
Type	☒	☐	☐	☐

Triaged By ..... M.B.M. .....

Dual Triage ..... of invalid cases