Issues arising in the treatment of depressed alcoholics with antidepressants

Introduction

Alcohol abuse and dependence are major public health problems across all demographics, characterised by recidivism, resulting in numerous medical and psychosocial complications. Indeed, Alcohol Use Disorders (AUDs) are widely recognised as carrying significant global morbidity and mortality; the World Health Organisation (WHO) identified alcohol as directly responsible for 3.3 million deaths per year worldwide, and contributing to the causation of more than 200 medical conditions, including neurological, gastrointestinal, cardiovascular and psychiatric disorders.[1]

Meanwhile, depression is the leading cause of suicide and currently the fourth highest disease burden on society in terms of its treatment costs, its effect on families and its impact on productivity in workplaces.[2] Depressed individuals use fewer planned appointments and more emergency hospital care for physical and mental health issues.[3] Worldwide projections by the WHO for the year 2030 identify unipolar major depression as the projected leading cause of disease burden.[4]

The co-occurrence of major depression in people entering treatment for alcohol dependence is common, representing an increased risk for morbidity and mortality, which negatively influences treatment outcomes. Indeed, the occurrence of a major depressive episode (MDE) or AUD doubles the risk of developing the other disorder.[5,6] Worryingly, the co-occurrence of the disorders bodes poorly for treatment outcomes; the presence of major depression has been associated with worse alcohol treatment outcomes, including lower self-reported efficacy in AUD treatment,[7] and a quicker time to relapse.[8] Significantly, patients with depression and AUD are at an increased risk of self-harm and suicide. Such patients lie at the intersection of Joiner's *Interpersonal-Psychological Model* of suicide –[9] depressive symptoms often representing the centre of their thwarted belongingness and perceived burdensomeness, while alcohol abuse signifies an acquired capability of suicide. Compared to the general population, having an AUD gives a 10-times increased risk of suicide,[10] while the relationship of depression and suicidal behaviour has been well documented.[11,12] For these reasons, such patients warrant careful evaluation and management.

In this essay, I aim to discuss the need for further research to understand and help those members of society who stand tragically at this juncture between alcohol abuse and depression. Having outlined the public health and societal burden posed by the conjunction of the two disorders, I demonstrate, through the case of a patient whom I met on my general practice attachment, the issues which arise in the treatment of depressed alcoholics. I discuss the biopsychosocial aspects which mean that much existing research concerning the relationship between alcohol misuse and depression do not apply to many patients who present to primary care. The implications of this in terms of the need for ongoing study of diagnosis and treatment of alcohol misuse and depression are highlighted throughout. It is hoped that this review will go some way towards portraying the common difficulties encountered in the primary care of the many members of society suffering from both depression and alcohol misuse.

Case Illustration – John

I was impelled to write this essay as a result of my experiences with a range of patients on psychiatric wards and in general practice. The insidious role which drug and alcohol abuse plays in so many lives, and the confusion surrounding the complex issues which arise in treatment of various psychiatric conditions in such lives, impacted me. The particular case described below is by no means unusual – in fact it seemed to be to be representative of many cases I encountered, not in its details but in the familiar patterns which alcohol weaves into the life of a seemingly 'normal', functioning member of society, and the uncertainty which such patterns introduce into the treatment of mental illness.

John* is a 27-year-old student who sees his GP for regular monitoring of his antidepressant medication. He has been taking fluoxetine for almost two years. He is currently also receiving occasional psychotherapeutic treatment from the student mental health services of his university.

John originally presented to his GP two years ago, seeking treatment for 'depression'. He had been seeing psychologists and therapists intermittently throughout his teen years and early twenties. This was originally in the form of CBT† for treatment of Obsessive Compulsive Disorder, followed by psychotherapy to treat what was diagnosed as a moderate depressive episode. For two weeks prior to seeking help from his GP, he had been suffering from anxiety as a result of an unwanted sexual experience, and potential rape, during a 'blackout' due to alcohol intoxication and ingestion of an 'unknown powder' while on holiday. He was concurrently being tested and treated by the sexual health team in a local hospital.

John described having experienced suicidal ideation on-and-off for several years. On further questioning, he described his life as having largely revolved around alcohol since he was 15. John portrayed a fairly 'happy' childhood in a supportive family, with several traumatic life events, including the separation of his parents, occurring during his teen years. He described the introduction of alcohol to his life as a 'defining moment' – he was able to separate his life into 'before' and 'after booze'. From an early age, he regularly abused alcohol to the detriment of his mood and relationships, but viewed it as an escape from his social awkwardness and existential insecurities. He said that it was likely that he had suffered memory 'blackouts' at least every other week for more than a decade. Nonetheless, he had successfully navigated his way through school and university and was still functioning well in most aspects of his life.

John had been hospitalised three times as a result of his drinking and drug abuse – twice being found by the police in a stupor and being treated conservatively in hospital, before ultimately suffering a seizure in public as a result of heavy drinking and the ingestion of large amounts of an unknown psychoactive powder at a festival. He had consulted his GP as a result of this latest hospitalisation, hoping to be treated for his ongoing depression.

John was referred to a local alcohol service and given literature on Alcoholics Anonymous groups. In this first consultation he was also prescribed 20 mg daily fluoxetine, which was increased to 40 mg several months later before being subsequently reduced back to the original dosage due to unwanted side-effects, including agitation and impulsivity. Over the past two years, his abuse of alcohol and other substances has continued, although he reports that some of his depressive symptoms have improved. He has insight into the way in which his alcohol use may be causing or worsening some of his symptoms of depression, and shows willingness to cut down or altogether stop his drinking. He presented to his GP to ask about the efficacy of his antidepressant medication and any potential risks related to his drinking.

John's case – significant points

John's case highlights a number of significant issues related to alcohol abuse and dependence, and its relationship with depression, particularly in a primary care setting. This essay aims to illustrate these points, and to review the literature which supports current guidelines in treating depressed alcoholic patients.

* Patient's name and personal details have been altered in order to maintain confidentiality

† Cognitive Behavioural Therapy

John appears to be a fairly typical example of a 'problem drinker'. It is thus important to question whether John actually had a diagnosis of alcohol dependence according to diagnostic criteria, and whether he fulfilled criteria for an affective disorder. It is clear that alcohol use disorders and mood disorders co-occur frequently;[13] together, they are associated with worse clinical and functional outcomes than when they occur individually.[14] The common aetiological patterns involved should be deciphered, since the assessment and management of people with co-occurring alcohol dependence and depressive disorders are significantly challenging. In John's case, did his depressive symptoms arise out of his alcohol abuse, or vice versa (or could they have arisen independently, or as a result of a common factor?)

It is not clear, based on guidelines, exactly how the general practitioner should have proceeded in this case. Current guidelines for treatment of alcohol and mood disorders in primary care will be assessed in this essay. Since John continued to drink heavily while taking his antidepressants, it should be asked what the effect of antidepressants is on addictive behaviours and alcohol abuse. There are many outstanding questions to be answered: should 'problem drinking' always be addressed before giving antidepressants? Does alcohol abuse reduce likelihood of compliance to antidepressant regimes? How does alcohol affect the required dosage of medications? And what role do psychotherapies and social interventions play?

The mode of John's presentation – originally to the Emergency Department, following an overdose, before self-referral to his GP – illustrates several points that must not be ignored. Since many of the risk factors for alcohol misuse are also risk factors for self-harm and suicide,[15] people with alcohol dependence or depression should be screened for other psychiatric symptoms, and for suicidality. Should there have been a clearer pathway to primary care treatment, and better communication between specialties?

Finally, it seems that some of John's depressive symptoms have improved over time. Is this in response to his antidepressant medication? There are fundamental questions to be reckoned with: who responds to antidepressants? Is the psychopathology of depressive symptoms in alcoholics different to other depressed patients? What are the common risk factors for alcohol abuse and depression? Thus, overall, through these questions arising out of John's case, this essay will aim to assess whether antidepressants should have been prescribed, whether John's alcohol abuse should have been addressed first, and whether antidepressants should be expected to have any effect in alcohol abusers. Gaps in the literature which have led to uncertainty in current guidelines will be highlighted throughout.

How is alcohol misuse measured?

'Problem drinking' is a major concern globally, as it can lead to serious long-term physical and mental health problems. It is clear to most primary care practitioners (and members of the public) that alcohol often mimics or worsens many of the symptoms of depression, including low mood, low energy, changes in appetite, weight or sleep pattern, poor concentration, feelings of guilt or worthlessness, and suicidal ideation and behaviour. Many people with depression may develop an alcohol problem as they 'self-medicate' in order to feel happier and more energetic.

The latest government guidelines recommend that both men and women do not drink more than 14 units of alcohol each week. Before the reduction in the limits for men from 21 to 14, over one third of men and one in five women exceeded the recommended number of weekly units. One in 15 men and one in 50 women suffer from alcohol dependence, and 40% of these dependents have symptoms resembling a depressive disorder.[16] 'Harmful drinking' is defined as a pattern of drinking that causes

damage to physical or mental health. 'Hazardous drinking' is defined as the regular consumption of 5 units per day for men, and 3 units for women. 'Binge drinking', meanwhile, is the consumption of more than 8 units (men) or 6 units (women) on one occasion. There is therefore some redundancy and confusion in how alcohol abuse is defined and diagnosed by general practitioners, not accounting for the fact that alcohol use is commonly under-reported.[17] What is explicit is that consuming excessive amounts of alcohol is dangerous for both physical and mental health.

There are two well-validated questionnaire that GPs use to screen and assess severity of alcohol misuse: the CAGE questionnaire screens for alcohol problems, and if positive, the Alcohol Use Disorders Identification Test (AUDIT) designed by the WHO assesses whether the patient is a hazardous drinker or has alcohol dependence. The ICD-10[‡] lays out a set of diagnostic guidelines for alcohol dependence, the most extreme category of AUD. Three or more of six factors must have been present at some time during the previous year for diagnosis. A retrospective assessment of John's history confirms his likely diagnosis as alcohol dependent.

What do the guidelines say?

GPs can have a major impact in reducing alcohol consumption by a simple technique called a brief intervention, and this is represented in the NICE guidelines for AUDs.[18] Brief interventions have been shown to produce reduction of up to one-third in reported weekly drinking.[19] However, such guidelines do not make clear the efficacy of such interventions in reducing alcohol intakes in patients with AUDs who are also depressed. Nor do they address the efficacy of common treatments for depression in alcoholics.

The NICE guidelines do mention patients who misuse alcohol and have comorbid depression or anxiety disorders – the alcohol misuse should be treated first, as this may lead to significant improvement in the depression and anxiety. If depression or anxiety continues after 3 to 4 weeks of abstinence from alcohol, the depression should be assessed, and referral and treatment considered in line with the relevant NICE guideline. The same sentiment is expressed on a patient advice page from the Royal College of Psychiatrists.[20] This states that most depressed drinkers will start to feel better within a few weeks of cutting out alcohol – hence the logical advice to tackle the alcohol problem first, before dealing with the depression afterwards if it has not lifted after a few weeks. The curious alcoholic is informed that they will 'probably feel fitter and brighter' in their mood after a few alcohol-free weeks, and that if feelings of depression do lift, 'it's likely that they were caused by your drinking'.

Of particular note is the NICE advice that antidepressants (including selective serotonin reuptake inhibitors [SSRIs]) are not used routinely for the treatment of alcohol misuse alone. Starkly missing from guidelines, however, is relevant advice for the common problem of depression concurrent with alcohol misuse, other than the recommendation for abstinence. The question remains unsettlingly unclear in cases such as John's – should antidepressants be prescribed for depressed alcoholics, and if not, then why? This is particularly relevant in patients with subclinical levels of alcohol misuse, who are often not represented in research, as outlined below.

Should antidepressants be prescribed to depressed alcoholics?

Major depression is generally responsive to pharmacological treatment; antidepressants can be life-saving in depressed patients at risk of suicide, and are now routinely prescribed, along with psychosocial interventions, for patients with moderate to severe major depressive disorder.[21] It is important to note, though, that the studies that supported approval of these medications typically

[‡] International Classification of Diseases, 10th Revision

excluded patients with comorbid alcohol dependence – thus, the early depression literature does not adequately address the efficacy of antidepressants in depressed alcoholics. This is despite depression frequently co-occurring with alcohol dependence.[22] A large proportion of patients excluded from randomised controlled trials have an AUD.[23] Further, while this paper focuses predominantly on the efficacy of antidepressants in depressed alcoholics, it must be noted that all patients in relevant trials received some form of psychosocial treatment. Their efficacy is not addressed in this review.

Early investigations into the use of antidepressants for treating depressed alcoholics gave disappointing results. These studies may be criticised for various reasons: for example, many failed to properly diagnose primary depression or to monitor pill compliance.[24] Most alarmingly, patients in many of the negative studies were likely to have been 'underdosed'. Some studies deliberately opted for lower antidepressant dosages due to the risk of alcoholics drinking during treatment, and hence experiencing unsafe medication-alcohol interactions. The question of whether this occurs is beyond the scope of this review, but it is noted here that it is likely that depressed alcoholics may actually require increased doses of antidepressant medication.[25]

More recently, and of clinical relevance in this country, a Cochrane review from 2017 concluded that there existed low-quality evidence supporting the clinical use of antidepressants in the treatment of people with co-occurring depression and alcohol dependence.[26] Antidepressants were found to have positive effects on some relevant outcomes related to depression, although most of these were found not to be significant when studies with high risk of bias were excluded.

One particular review[27] concluded that there is some evidence that antidepressants can be effective in patients with alcohol problems. However, it is important to examine the methods used to score depression in studies included in such a review. In this case, the statistical significance of the findings depended on which scale for measuring depression was used, highlighting the limitation of such scoring systems both in research and the clinical setting.

An important question is whether antidepressants may aid specifically in the misuse of alcohol in depressed alcoholics. It seems intuitive that, since alcohol (despite its depressant effects) is thought to be used in many patients to self-medicate depressive symptoms, the use of antidepressants in aiding recovery from depression should lead to a decreased intake of alcohol. Once quality of life is improved, previously neglected activities should be recommenced – thus negating one of the criteria for AUD. With respect to drinking outcomes, results are, however, inconsistent and potentially negative as to whether antidepressants exert any direct effects in reducing drinking.[24] Conflicting findings of SSRIs reducing drinking in depressed alcoholics have mirrored reports from clinical trials of SSRIs for reducing alcohol intake in alcoholics, irrespective of depression.[28,29] To summarise, most results illustrate that giving antidepressants (with psychosocial treatments) to depressed alcoholics may alleviate depression, but in most cases has little direct impact on drinking over placebo.

On the basis of clinical trials, recommendations in the US have suggested that concurrent substance abuse should not be a barrier to treating depression.[30] However, clinicians working with substance-dependent patients are often reluctant, for a variety of reasons, to initiate antidepressant treatment.[31] This includes concerns about confusing substance-induced depressive symptoms with true depressive symptoms. More evidence is needed in order to guide treatment. From this point on, the aims of this review are (rather than more in-depth assessment of current trials on the efficacy of antidepressants) to pinpoint how alcohol misuse and depression are intertwined, in the hope that such understanding will aid in future avenues of research into the treatment of depressed alcoholics.

Which comes first – alcohol abuse or depression?

The efficacy of antidepressants in those suffering from alcohol misuse remains unclear. Several questions must be addressed. Firstly, it is important to understand whether alcohol misuse is more likely to precede, or result from, depression. This may help to address why most clinical trials have conveyed inconsistent findings.

It has commonly been considered that identifying the aetiology of the depression in alcoholics is vital for determining the course of the illness and the optimal treatment approach. It would seem logical that in primary depression (not due to the effects of alcohol), depressive symptoms would persist even after treating alcohol dependence – in such cases, treatment with antidepressant medication would be warranted. In cases where alcohol is self-medicating a primary depression, alleviating depression should positively impact the AUD and thus reduce drinking. On the other hand, if the depression is a clear result of alcohol misuse, it should be questioned whether an antidepressant would have any therapeutic impact. Regardless of the aetiology, as many as 80% of patients seeking treatment for an AUD report distress from psychiatric symptoms (most commonly depressive symptoms); treating depressive symptoms in alcoholics remains an important and misunderstood issue. GPs are expected to make decisions about how to treat depression in the presence of active alcohol dependence, without the benefit of observing the patient in an extended period of abstinence, thus relying on patients' reports in order to determine the temporal sequence of depressive symptoms in relation to excessive drinking. An accurate diagnosis of primary and secondary depression is currently often unobtainable; a better understanding of the aetiology in this complex interplay of psychosocial events and situations with the biological impacts of alcohol use in the short and long term is needed.

There are, however, a range of issues which arise with the co-occurrence of substance use disorders and psychiatric symptoms which stand in the way of such an understanding. An expert review from Schuckit (2006)[32] details the potential reasons for such comorbidity. Firstly, the combination of SUDs and psychiatric disorders may represent two or more independent conditions, each of which is likely to run its own unique clinical course. In such a case, both conditions must be treated comprehensively. Such a combination could occur either through chance alone, or may be a consequence of the same predisposing factors affecting the risk of both conditions (such as childhood stresses, or a genetic predisposition). Secondly, the first disorder could influence the development of the second in such a way that the additional disorder then runs its own independent course (i.e. substance abuse could unmask a latent predisposition towards a psychiatric disorder, or cause permanent changes in the brain). In such a case, both conditions should still be treated for as long as is necessary. Another scenario is the second condition developing through the effort of somebody trying to diminish the problems associated with a first condition (i.e. self-medication). Finally, some syndromes may represent a temporary picture as a direct consequence of intoxication or withdrawal conditions. Distinguishing between these scenarios remains an important challenge to researchers and clinicians, as the distinction between them has important implications for treatment.

One longitudinal study showed that both alcohol dependence and depression pose a significant risk for the development of the other disorder at one year.[33] Both paths to dual diagnosis of alcohol dependence and depression were defined by dose-response relationships; a greater degree of symptoms of the first diagnosis at baseline predicted more strongly the appearance of the second diagnosis. It was found, however, that the risk of developing depression after the onset of an AUD is higher than the risk of the converse occurring. This is consistent with results from the National Comorbidity Survey in the US – primary alcohol dependence is more common than primary depression amongst subjects suffering from both disorders.[34] Importantly, it was also found that subclinical levels of alcohol dependence and major depression significantly predicted the future development of the

other disorder, implying that recognising and treating symptoms that do not meet full diagnostic criteria may prevent the emergence of secondary psychiatric disorders. This is an important point to emphasise for psychiatry in general.

How, then, should treatment proceed in cases of comorbidity? One paper offered several different conceptual approaches: sequential, parallel or integrated.[35] The authors note that trying to sequentially address co-occurring AUD and depression, regardless of the aetiology, may fail to recognise a potentially reciprocal connection between each disorder, and thus handicap the treatment of both. They therefore offer an integrated model for treatment of dually-diagnosed patients. The data on the integrated treatment for comorbid AUD and depression remains limited, though some positive results for such an approach have emerged.[36,37] In order to support such an approach, more research is needed into the way in which the treatment of depression leads to an improvement in alcohol misuse, and vice versa.

Are antidepressants addictive, and could they exacerbate pre-existing addiction?

Patients with AUDs represent an at-risk group. Since it seems unlikely, as outlined above, that antidepressants directly decrease alcohol intake in depressed alcoholics, it must be questioned whether they could actually have a negative impact, before their use is endorsed by guidelines. Thus, there are several important issues to be addressed. Firstly, it should be questioned whether antidepressants could contribute to addiction – either by directly exacerbating alcohol abuse, or by increasing the 'addictive state'. There are a number of hypothetical mechanisms within a biopsychosocial model of how this could take place. Could antidepressants affect the biochemical pathways involved in substance dependence models? Alternatively, could they alter the psychological state of alcohol abusers? Or is there a potential social mechanism through which becoming diagnosed as depressed, and treated for depression, increases helplessness in alcoholics? A second question which must be answered is whether antidepressants themselves are addictive, and hence a danger to an already vulnerable population. Finally, how common are withdrawal or discontinuation symptoms on stopping antidepressants, and how often does relapse occur? Withdrawal from antidepressants, or relapse back into a depressive state, may have the potential to worsen alcohol abuse.

In all areas of medicine, public opinion is important in determining both uptake and efficacy of treatment regimens. This may be particularly relevant in psychiatry. In a 1996 national poll, 78% of the public regarded antidepressants as addictive.[38] However, in actual clinical practice, while withdrawal or discontinuation symptoms have long been recognised with antidepressants, other features of addiction such as tolerance and compulsive use are exceptionally rare.[39] The pharmacodynamics profiles of most antidepressants and the absence of acute 'desirable' effects, commonly a pre-requisite for a substance to be considered 'addictive', make addiction theoretically unlikely. Clinical problems are thought to occur mostly when patients prematurely stop antidepressant treatment.

However, in recent years, the assumption that antidepressants should not be considered addictive or a danger to patients addicted to other substances has been questioned. Firstly, there was a recent call from the NHS for guidelines to be revised over antidepressant withdrawal symptoms. This was the result of a 2018 systematic review which found that over half of people who attempt to come off antidepressants experience some withdrawal symptoms.[40] This paper suggested that current guidelines underestimate the severity and duration of antidepressant withdrawal, with significant implications in clinical care. The authors went as far as publishing online a letter they addressed to the president of the Royal College of Psychiatrists which challenged the College of burying inconvenient

data related to the misuse of antidepressants.[41] However, it is notable that the review included evidence from online surveys, which may be susceptible to selection bias.

Another recent paper compared current views towards antidepressants and benzodiazepines.[42] The authors noted that, while the withdrawal reactions to SSRIs appear to be similar to those experienced in benzodiazepine withdrawal, there is a clinical tendency to refer to a dependence syndrome in the case of benzodiazepines, but not in SSRIs. Does this discrepancy represent an irrationality in the regard of SSRIs not being involved in addiction? And if so, may they in fact play an insidious role in the continued addiction experienced by patients with AUDs who are treated for their depressive symptoms with antidepressants? These questions remain unanswered, though much research is being conducted on the issue of abuse of antidepressants.[43]

The inflamed mind – an alternative model for depression in alcoholics

The rationale for the pharmacological treatment of depression relies on the assumed important role which serotonin pathways play in the depressive state. Pre-clinical studies have also demonstrated the role of serotonin pathways, particularly related to dopaminergic function (which mediates alcohol-induced reward) in the development and maintenance of alcohol-seeking behaviours.[44] However, the lack of evidence for a positive effect of SSRIs on alcohol intake fails to support this theory. Perhaps a different model is required to explain the appearance of depressive symptoms in alcohol misuse. Current pharmacological treatments for alcoholism, such as naltrexone and ondansetron, are beyond the scope of this review. In alcohol dependence, as with depression and all of psychiatry, more research is needed to understand more clearly the molecular genetic differences, and the interactions of these differences with the environment, that typify a particular alcoholic subset. It is posited here that different subsets of the population may benefit from different treatments, depending on the aetiology of their alcohol dependence and depression.

A recent *Lancet* article described how research in the last two decades has highlighted the link between depression and inflammation of the body and brain.[45] The author explains how mental disorders such as depression may have their roots in the immune system, and outlines a future revolution in which treatments specifically target the inflammatory state. Could such an approach also help to explain the development of alcohol dependence, and the causation of depressive symptoms in such an inflamed state? If so, it may go some way towards explaining why traditional antidepressants do not improve depression in a large subset of depressed alcoholics. Indeed, alcohol has been shown to significantly increase the translocation of lipopolysaccharide from the gut. Chronic alcohol use then impairs not only gut and liver functions, but also the interactions between organs, and may lead to persistent systemic inflammation.[46] Circulating cytokines are now being considered as important mediators of the gut-brain communication, as they can cross the blood brain barrier, reaching the central nervous system and possibly inducing the neuroinflammation that is associated with changes in mood, cognition, and drinking habits.[47] Details of these developments are beyond the scope of this review, but are intended to represent the possibility that paradigm shifts in our understanding of depression and alcohol dependency may pave the way for novel therapeutics to target both alcohol dependence, and the depressive symptoms which often arise in such a state.

Conclusions

In conclusion, as with many areas of psychiatry, there remain more questions than answers. In John's case, it is not clear whether his treatment with antidepressants had a positive impact on the course of his depression or alcohol misuse. This is an area in which clinical outcomes are intrinsically difficult

to measure. Thankfully, he shows a continued insight into his alcohol misuse, and continues to interact with health care teams. But many are not so lucky.

Despite the high rate of alcohol problems in depressed patients, and depression in alcoholics, there is a general dearth of treatment research in this area. It is here concluded that alcohol problems and depression occur together on a worrying scale, and are associated with adverse clinical and health care utilisation outcomes. It should be tentatively stated that antidepressants can effectively treat depression in the setting of alcohol misuse. It seems unlikely that antidepressant treatment leads to a decrease in alcohol use in depressed alcoholics. The clinical usefulness of the findings from this review are limited by the fact that studies are principally conducted in patients with the most extreme degrees of alcohol abuse, and in a narrow scope of clinical settings. In order to more generally answer the clinical questions posed in this essay, the prevalence and effects of varying levels of alcohol use and abuse among depressed patients treated in a variety of clinical settings need to be studied. Future GPs provided with this information will be more empowered to accurately assess the impact of varying levels of alcohol use on their patients' depression and overall quality of life, and to offer better therapies to minimise this impact.

Our understanding of depression and alcohol abuse, as with other disorders in psychiatry, remains firmly in its infancy. This is both a frustrating and exciting time for psychiatry. Many future research avenues, such as the inflammatory model of psychiatric disorders (briefly outlined above), remain tantalisingly open. What is clear is that both researchers and clinicians must be open-minded to new paradigms for diagnosis and treatment of psychiatric disorders. It is hoped that one day, a more integrated model of psychiatry will mean that patients like John are given a more transparent explanation for their own mental health, and a clearer outline for their treatment. As the great medical writer Oliver Sacks noted, we require '*meaning, understanding, and explanation'*. By gaining an insight into the patterns weaved into their lives by alcohol and depression, John, like many of us, will gain hope, and '*the sense of a future'*.[48]

Word count: 4987

References

[1] World Health Organization. (2014). Management of Substance Abuse Unit. Global status report on alcohol and health. *World Health Organization (WHO)*. Available online at: http://apps.who.int/iris/bitstream/10665/112736/1/9789240692763_eng.pdf [Accessed 3rd February 2019]
[2] Pilling, S., Anderson, I., Goldberg, D., Meader, N., Taylor, C., & Two Guideline Development Groups. (2009). Depression in adults, including those with a chronic physical health problem: summary of NICE guidance. BMJ, 339(10.1136).
[3] Dorning, H., Davies, A., & Blunt, I. (2015). Focus on: People with mental ill health and hospital use. Exploring disparities in hospital use for physical healthcare. Research summary. London: The Health Foundation and Nuffield Trust. Available at: www.qualitywatch.org.uk/focus-on/physical-and-mentalhealth (accessed on 23 April 2018).
[4] Lépine, J. P., & Briley, M. (2011). The increasing burden of depression. Neuropsychiatric disease and treatment, 7(Suppl 1), 3.
[5] Boden, J. M., & Fergusson, D. M. (2011). Alcohol and depression. Addiction, 106(5), 906-914.
[6] Gilman, S. E., & Abraham, H. D. (2001). A longitudinal study of the order of onset of alcohol dependence and major depression. Drug and alcohol dependence, 63(3), 277-286.
[7] Greenfield, B. L., Venner, K. L., Kelly, J. F., Slaymaker, V., & Bryan, A. D. (2012). The impact of depression on abstinence self-efficacy and substance use outcomes among emerging adults in residential treatment. Psychology of Addictive Behaviors, 26(2), 246.
[8] Greenfield, S. F., Weiss, R. D., Muenz, L. R., Vagge, L. M., Kelly, J. F., Bello, L. R., & Michael, J. (1998). The effect of depression on return to drinking: a prospective study. Archives of general psychiatry, 55(3), 259-265.
[9] Joiner, T. (2007). Why people die by suicide. Harvard University Press.
[10] Wilcox, H. C., Conner, K. R., & Caine, E. D. (2004). Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug and alcohol dependence, 76, S11-S19.
[11] Bailey, R. K., Patel, T. C., Avenido, J., Patel, M., Jaleel, M., Barker, N. C., ... & Jabeen, S. (2011). Suicide: current trends. Journal of the National Medical Association, 103(7), 614-617.
[12] Sher, L. (2006). Alcoholism and suicidal behavior: a clinical overview. Acta Psychiatrica Scandinavica, 113(1), 13-22.
[13] Teesson, M., Hall, W., Lynskey, M., & Degenhardt, L. (2000). Alcohol-and drug-use disorders in Australia: Implications of the National Survey of Mental Health and Wellbeing. *Australian and New Zealand Journal of Psychiatry*, *34*(2), 206-213.
[14] Zarkin, G. A., Bray, J. W., Aldridge, A., Mills, M., Cisler, R. A., Couper, D., ... & O'Malley, S. (2010). The impact of alcohol treatment on social costs of alcohol dependence: results from the COMBINE study. *Medical care*, *48*(5), 396.
[15] Pompili, M., Serafini, G., Innamorati, M., Dominici, G., Ferracuti, S., Kotzalidis, G. D., ... & Sher, L. (2010). Suicidal behavior and alcohol abuse. *International journal of environmental research and public health*, *7*(4), 1392-1431.
[16] Institute of Alcohol. (2009). Excessive and problem drinking in England & Wales.
[17] Office for National Statistics: Adult drinking habits in Great Britain: 2017. Available online at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/bulletins/opinionsandlifestylesurveyadultdrinkinghabitsingreatbritain/2017 [Accessed 3rd February 2019]
[18] National Institute for Clinical Excellence. (2011). Alcohol-use disorders: diagnosis and management.
[19] Kaner, E. F., Beyer, F. R., Muirhead, C., Campbell, F., Pienaar, E. D., Bertholet, N., ... & Burnand, B. (2018). Effectiveness of brief alcohol interventions in primary care populations. Cochrane database of systematic reviews, (2).
[20] Royal College of Psychiatrists. Alcohol and Depression. Available at: https://www.rcpsych.ac.uk/mental-health/problems-disorders/alcohol-and-depression [Accessed 3rd February 2019]
[21] Anderson, I. M. (1998). SSRIs versus tricyclic antidepressants in depressed inpatients: A meta-analysis of efficacy and tolerability. Depression and Anxiety, 7(S1), 11-17.
[22] Swendsen, J. D., & Merikangas, K. R. (2000). The comorbidity of depression and substance use disorders. Clinical psychology review, 20(2), 173-189.
[23] Partonen, T., Sihvo, S., & Lönnqvist, J. K. (1996). Patients excluded from an antidepressant efficacy trial. The Journal of clinical psychiatry, 57(12), 572-575.
[24] Pettinati, H. M. (2004). Antidepressant treatment of co-occurring depression and alcohol dependence. Biological Psychiatry, 56(10), 785-792.

[25] Mason, B. J., Kocsis, J. H., Ritvo, E. C., & Cutler, R. B. (1996). A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. Jama, 275(10), 761-767.
[26] Agabio, R., Trogu, E., & Pani, P. P. (2018). Antidepressants for the treatment of people with co‐occurring depression and alcohol dependence. Cochrane Database of Systematic Reviews, (4).
[27] Sullivan, L. E., Fiellin, D. A., & O'Connor, P. G. (2005). The prevalence and impact of alcohol problems in major depression: a systematic review. The American journal of medicine, 118(4), 330-341.
[28] Pettinati, H. M., Kranzler, H. R., & Madaras, J. (2002). The status of serotonin-selective pharmacotherapy in the treatment of alcohol dependence. In Recent Developments in Alcoholism (pp. 247-262). Springer, Boston, MA.
[29] Pettinati, H. M., Oslin, D., & Decker, K. (2000). Role of serotonin and serotonin-selective pharmacotherapy in alcohol dependence. CNS spectrums, 5(2), 33-46.
[30] Whooley, M. A., & Simon, G. E. (2000). Managing depression in medical outpatients. New England Journal of Medicine, 343(26), 1942-1950.
[31] Nunes, E. V., & Levin, F. R. (2004). Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. Jama, 291(15), 1887-1896.
[32] Schuckit, M. A. (2006). Comorbidity between substance use disorders and psychiatric conditions. Addiction, 101, 76-88.
[33] Gilman, S. E., & Abraham, H. D. (2001). A longitudinal study of the order of onset of alcohol dependence and major depression. Drug and alcohol dependence, 63(3), 277-286.
[34] Kessler, R. C., Crum, R. M., Warner, L. A., Nelson, C. B., Schulenberg, J., & Anthony, J. C. (1997). Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Archives of general psychiatry, 54(4), 313-321.
[35] DeVido, J. J., & Weiss, R. D. (2012). Treatment of the depressed alcoholic patient. Current psychiatry reports, 14(6), 610-618.
[36] Hides, L. M., Elkins, K. S., Scaffidi, A., Cotton, S. M., Carroll, S., & Lubman, D. I. (2011). Does the addition of integrated cognitive behaviour therapy and motivational interviewing improve the outcomes of standard care for young people with comorbid depression and substance misuse?. Medical Journal of Australia, 195(3), S31.
[37] Pettinati, H. M., Oslin, D. W., Kampman, K. M., Dundon, W. D., Xie, H., Gallis, T. L., ... & O'Brien, C. P. (2010). A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. American Journal of Psychiatry, 167(6), 668-675.
[38] Priest, R. G., Vize, C., Roberts, A., Roberts, M., & Tylee, A. (1996). Lay people's attitudes to treatment of depression: results of opinion poll for Defeat Depression Campaign just before its launch. *Bmj*, *313*(7061), 858-859.
[39] Haddad, P. (1999). Do antidepressants have any potential to cause addiction?. Journal of Psychopharmacology, 13(3), 300-307.
[40] Davies, J., & Read, J. (2018). A systematic review into the incidence, severity and duration of antidepressant withdrawal effects: Are guidelines evidence-based?. Addictive behaviors.
[41] Letter may be accessed online: http://cepuk.org/2018/03/01/royal-college-psychiatrists-challenged-burying-inconvenient-antidepressant-data/ [Accessed 3rd February 2019]
[42] Nielsen, M., Hansen, E. H., & Gøtzsche, P. C. (2012). What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re‐uptake inhibitors. Addiction, 107(5), 900-908.
[43] Evans, E. A., & Sullivan, M. A. (2014). Abuse and misuse of antidepressants. Substance abuse and rehabilitation, 5, 107.
[44] Johnson, B. A. (2004). Role of the serotonergic system in the neurobiology of alcoholism. CNS drugs, 18(15), 1105-1118.
[45] Bullmore, E. (2018). Inflamed depression. The Lancet, 392(10154), 1189-1190.
[46] Wang, H. J., Zakhari, S., & Jung, M. K. (2010). Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. World journal of gastroenterology: WJG, 16(11), 1304.
[47] Leclercq, S., de Timary, P., Delzenne, N. M., & Stärkel, P. (2017). The link between inflammation, bugs, the intestine and the brain in alcohol dependence. Translational psychiatry, 7(2), e1048.
[48] Sacks, O. (2012). Altered states: self-experiments in chemistry. The New Yorker, 27.