Editors' view

Drugs for addiction: a therapeutic area in need of a 'shot in the arm'

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CDW: I was twenty-five. And erm, I remembered as I drank it (my first whisky) feeling, you know, this is the answer, this is it, you know, why have I waited so long not to drink, you know, I've come home. And from thereon in I drank very heavily, very quickly, getting to two bottles of gin a day and the rest.

SL: But when you drank it you recognized it, your body recognized it.

CDW: My body recognized it, and my genes recognized it, I suppose.

SL: But you thought you could control it?

CDW: No, I never thought I could control it. I was on a path for destruction.

Excerpt from Clarissa Dixon Wright's appearance on BBC Radio 4 Desert Island Discs (<http://www.timpardoe.co.uk/cdw.asp>)

According to the UK National Health Service, addiction is not having control over doing, taking or using something harmful (<http://www.nhs.uk/conditions/addictions>). The subject has historically been the province of moralists and of social reformers, and only in recent years has the science underlying addiction gained prominence. Central to our understanding of the subject is the issue of the brain substrate of 'control'. While personal, emotional, psychological and environmental factors are important in preventing addictive behaviour, or in breaking the cycle of addiction once it has begun, it is now clear that changes in behaviour can be facilitated by pharmacological and psychosocial interventions. Moralistic attitudes which at worst deny the efficacy of such interventions, or at best question whether healthcare resources should be invested into such interventions, have however been hard to break down and unfortunately still have considerable influence on healthcare planning, research and delivery as well as on drug policy.

Our understanding of the neurobiological substrates of addictions is the most extensive and robust across the whole spectrum of mental disorders, in large part because it is the field of psychiatric research in which animal models are most valid and fit for translational purpose. Thirty years of this research point to significant gene-environment interactions, just as is the case with numerous other diseases.

The information gained from addiction research has at times resulted in knowledge-based drug development (e.g. naltrexone for addiction to alcohol), an impressive feat in the field of non-neurological brain disorders, where medicinal developments have been mostly based on serendipity. Further, advances in mechanistic understanding have allowed interesting and useful comparisons to be drawn between addiction to drugs/alcohol and other syndromes such as obesity [1] and gambling [2], which seem to be maintained by similar brain circuits.

Despite such advances in addiction science, big pharma medicinal development and governmental policies have generally not kept up with the implications of this research, except for addictions to nicotine (where substitution and reduction of craving are seen as important tools) and perhaps alcohol (reduction of craving). In some quarters, the medicalization of addictions is still lamented and thought to be unnecessary. In industry, a mixture of poor forecast returns, fear of law suits and brand damage are often mentioned as reasons for not getting involved in this area, where public prejudice still holds much sway.

The cost to society related to use of drugs of abuse is clear. The main finding of a report published in 2009 in the US (<http://www.casacolumbia.org/articlefiles/380-ShovelingUpII.pdf>) was that the cost of addictions to government was \$467.7 billion in 2005, and for every dollar spent '95.6% (\$357.4 billion) went to shovel up the consequences and human wreckage of substance abuse and addiction, only 1.9% went to prevention and treatment,

0.4% to research, 1.4% to taxation and regulation, and 0.7% to interdiction'. The year after the above report was published (2010), it was estimated that the US government spent \$15 billion on the international 'war on drugs' as part of a total yearly 'war on drugs' expenditure of almost \$90 billion that included federal and state expenditure on domestic law enforcement (<http://www.countthecosts.org/sites/default/files/AWDR.pdf>). In the UK, it is estimated that drug and alcohol abuse costs £36 billion per annum (<http://www.centreforsocialjustice.org.uk/UserStorage/pdf/Pdf%20reports/addict.pdf>). This is therefore a global issue that constitutes a large economic drain on resources in many nations, and therefore merits urgent attention.

In spite of these figures, the annual budget of the US flagship research institute, the National Institute on Drug Abuse (NIDA), is about \$1 billion per year- a very small fraction of the cost to society as a whole. Equally concerning is the fact that NIDA funding is estimated to represent about 80% of the world's expenditure on research on drugs of abuse. In the UK for example, the Medical Research Council allocated about £6.5 million on addiction research between 2009 and 2010, which actually represented a large increase on previous levels of expenditure!

The present issue of the BJCP is dedicated to the clinical pharmacology of addictions, a subject which is central to the further development of therapeutic agents in this important but hitherto neglected field of medicine. Current clinical practice is critically summarized looking at strategies for detoxification across a number of substances including alcohol [3] and nicotine smoking [4], as well as different stages in treating opioid dependence [5, 6]. The (clinical) pharmacology of acamprosate is reviewed by Kalk & Lingford-Hughes [7]. This is the only mainstream medicine used in the treatment of alcohol addiction for which the mechanism of action that delivers efficacy remains unclear. Kunhoe *et al.* [8] and Hulse [9] describe how suitable pharmaceutical delivery has the potential to transform the way a medicine is used. Just as depot antipsychotics improved the treatment of schizophrenia in people who were likely to have poor treatment adherence but still consented to treatment, depot naltrexone may prove to be a significant advance in maintaining abstinence in people with previous addiction to opioids or alcohol. Less advanced in the development cycle, the same research group proposes the use of flumazenil infusions in people who are dependent on benzodiazepine ligands or have developed tolerance to their positive effects and have difficulty in coming off them [10]. Lader [11] resolutely reminds us that this addiction is mostly iatrogenic and that professional circumspection in prescribing would prevent this. The problem here is that there is a lack of medicines that have the same efficacy as benzodiazepine ligands, and also that people can readily access much more harmful and less efficacious substances like alcohol. Again the issue seems to be one of balance. Ben-

zodiazepine ligands clearly can be harmful when prescribed irresponsibly, but blanket algorithms regarding their therapeutic use will deny these useful medicines to people in whom the benefits outweigh their risks. A similar debate is presented around the use of ketamine in chronic pain [12, 13] and especially in chronic regional pain syndrome, another drug which is efficacious in selected situations and patients but has high addictive and potentially toxic capability.

We are also reminded of the difficulties facing clinicians when prescribing stimulants for attention deficit hyperactivity disorder (ADHD) in adults who also have a history of drug abuse. Stimulants are first line choice in adult ADHD (NICE guideline: <http://guidance.nice.org.uk/CG72/NICEGuidance/pdf/English>), but if the diagnosis is made in adulthood much of the personal and social damage of this condition has already set in, so the future here relies on better early recognition and efficacious treatment in childhood and adolescence. It is perhaps not surprising that many youths with severe ADHD end up self-medicating with alcohol and drugs, finding that these and other drugs allow them to function better. However, we are also reminded that this is a bidirectional and not unidirectional relationship. In the UK, ADHD is a clear example of discrimination against people with psychiatric disorders. NICE guidelines with a solid evidence base exist, yet many commissioners refuse to commission services or even close down good existing adult services, not appreciating the profound impact of this condition both at personal and societal levels. This clear exposition by de los Cobos *et al.* [14] shows that decisions on how to treat should remain clinical and tailored to individuals, and that prolonged release stimulants and atomoxetine can also have an impact in people with comorbid substance misuse.

Some readers may be surprised to see how far thinking on the biology of pathological gambling has progressed. Grant *et al.* [15] summarize the state of play in treating pathological gambling. This is important not only for people who have the condition but may also significantly aid a paradigm shift in the public understanding of addictions.

The issue also considers new treatment paradigms that are not in the clinic as yet. Kosten [16] describes the progress of vaccines, and by the time, or soon after, this issue is published, some of the trial results may be available. Future pharmacological treatments that reformulate the problems in terms of modulating positive and negative reinforcement, and of decreasing vulnerability to becoming addicted, are presented by Forray & Sufouglu [17]. This reformulation is likely to be one of the ways forward in redeveloping psychiatric classification of these disorders.

Altogether this is a very stimulating issue that demonstrates that the field is thankfully alive throughout the world but on the whole starved of funds. Some of the simpler developments (such as pharmaceutical reformulation) that would be rapid in a well funded area are taking a

long time to materialize. The most important developments will however be based on an increasing understanding that there are physical substrates to addictions that can be successfully modulated pharmacologically.

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