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Abstract
Cravings, intense desires to experience the effects of a drug, are widely regarded as significant impediments to overcoming addiction, although their role in relapse may be overstated. Scientists and clinicians wish to better understand the neurobiological and cognitive basis of craving so that they may develop psychotherapeutic, pharmacological and other medical methods to reduce craving and thereby drug use. The conduct of such research raises significant ethical issues. When recruiting individuals and conducting this research, scientists need to ensure that substance dependent participants have the capacity to provide free and uncoerced consent. This is especially the case in studies in which dependent participants are given their drug of addiction or provided with other inducements to participate (e.g. financial incentives) that may undermine their ability to fully consider the risks of participation.
Treatments for addiction that seek to reduce cravings may also carry risks. This includes psychotherapeutic approaches, as well as pharmacological and medical treatments. Clinicians need to consider the risks and benefits of treatment and carefully communicate these to patients. The desire to reduce urges to use drugs should not be employed to justify potentially harmful and ineffective treatments. The safety and effectiveness of emerging treatments should be assessed by well conducted randomized controlled clinical trials.

1. Introduction

Individuals with a substance use disorder (SUD) who succeed in stopping their drug use often report strong desires or "cravings" for their drug of dependence that may last for some months after achieving abstinence. Cravings are often viewed as a major cause of relapse to drug use (Tiffany, 1990 and Tiffany, 1998). Craving may emerge in response to cues associated with drug use (cue-reactive craving) or as a result of aversive withdrawal symptoms (Drummond, Litten, Lowman, & Hunt, 2000).

Craving is often described as synonymous with addiction. On this view, if we eliminate cravings, we can cure addiction. However, the relationship between drug use and the experience of craving is not straightforward (Drummond et al., 2000). Drug use commonly occurs in the absence of any strong desire to use drugs as a form of habitual or automatic behaviour (Hyman, 2005 and Tiffany and Conklin, 2000). Craving is rarely identified as a major precipitant by relapsed drug users (Tiffany & Conklin, 2000) and it is observed in those who significantly reduce consumption just as frequently as those who abstain (e.g. smoking) (Tiffany, 1998). There is also limited evidence of a correlation between craving and drug use in cue-reactivity studies (Tiffany & Conklin, 2000).

While cravings may not explain all relapses, they may still play a major part in the continued drug use in some persons. In so far as this is true, reducing the experience of these strong motivations for drug use will reduce drug use and improve social functioning among addicted persons. There are a variety of psychological, pharmacological and social methods that have been adopted to reduce craving-induced

relapse. Within the 12-step, self-help tradition of Alcoholics and Narcotics Anonymous, recovering persons are encouraged to avoid situations that evoke craving (Humphreys, 2004). Other psychotherapies, such as cognitive behaviour therapy (Morgenstern & Longabaugh, 2000), mindfulness (Westbrook et al., 2011) and cue-exposure (Kaplan, Heinrichs, & Carey, 2011), attempt to change patients' responses so that craving does not inevitably lead to drug use.

Pharmacological treatments may be used to control drug craving in various ways. They are often used to reduce the severity of aversive symptoms during medically-supervised withdrawal from the drug of dependence, such as nicotine replacement therapy for smoking, long-acting benzodiazepines during alcohol withdrawal, and clonidine for opioid withdrawal (Amato et al., 2005 and Lingford-Hughes et al., 2004). Pharmacological assistance may also be provided over longer periods to prevent cravings from leading to relapse to addictive drug use, especially during the first three months of abstinence when relapse is most likely to occur (Anton et al., 2006 and O'Brien, 2005).

In this paper we consider some key ethical issues that arise in the research and treatment of craving. First, we discuss ethical issues that may arise in experimental studies of craving in three participant populations: non-dependent volunteers; actively dependent persons; and formerly dependent persons. Second, we outline ethical issues that may arise in trialling novel therapies that aim to reduce craving or prevent relapse by reducing the likelihood of reinstatement of addictive drug use. Lastly, we describe ethical issues that may arise in the use of long-acting relapse prevention treatments.

2. Ethical issues in laboratory studies of craving

Our analysis of ethical issues in craving research is based on concepts outlined in key contemporary approaches to protecting the rights of research participants in social and medical research (Economic and Social Research Council, 2005, National Bioethics Advisory Commission, 1999 and NHMRC, 2007). These concepts are underpinned by a basic respect for persons, which is taken to entail the following obligations on researchers (Beauchamp and Childress, 2009 and Faden et al., 1986):

1.Participation in research must be voluntary and informed consent must be obtained from participants before they enter a research study.
2.Researchers must respect the privacy of participants, and take every reasonable effort to protect the confidentiality of information that they obtain.
3.Researchers must avoid any foreseeable risk of harm to the participant (non-maleficence), and if possible, maximise the benefits of research participation (beneficence). The risk from study participation may be warranted if participants are likely to derive significant benefit, assuming that (1) is satisfied.

Human studies of craving are most often conducted on actively addicted participants or participants who have been addicted and are currently abstinent. These studies raise a number of salient ethical issues because this is a vulnerable population. We have discussed these issues in more detail elsewhere (Miller, Carter, & Hall, 2010). In this paper, we focus on those ethical issues raised specifically by human craving studies that involve the administration of small doses of drugs or the presentation of drug-related cues (e.g. injecting equipment) to addicted persons in order to examine their effects on

self-reported craving and objective measures (e.g. physiological, behavioural or neurobiological) that are believed to be correlated with craving, such as, changes in brain function revealed by neuroimaging technologies (e.g. Goudriaan et al., 2010, Kling et al., 2000, Martin-Soelch et al., 2001 and Sell et al., 1999). Cue-reactivity in the absence of an opportunity to consume the drug of addiction does not have the same salience as cue-reactivity when drug consumption is possible. Cue-reactivity studies will therefore often involve the administration of small amounts of the addicted drug. Measuring drug consumption in the laboratory allows researchers to validate measures of self-reported craving and is seen as essential in designing clinical trials of new treatments (Meyer, 2000).

2.1. Studies of craving in non-addicted participants

Giving addictive drugs to drug-naïve participants exposes them to the effects of a substance that they may not have otherwise used. Non-addicted individuals may take part in craving research as control participants or in studies of the effects of drug consumption (usually alcohol) on expectancies of the effects of future consumption. Follow-up studies suggest that this is not a major risk: providing drug-naïve participants with an appropriate dose of an addictive drug in a laboratory under medical supervision does not appear to increase the subsequent risk of addiction or harmful drug use (Adler, 1995, Kirulis and Zacny, 1998 and Wood and Sher, 2000). Studies of the effects of alcohol in college students, for example, do not raise this concern. Participants in these studies usually do not meet criteria for alcohol dependence, although most are regular binge drinkers, if not heavy drinkers. A potential benefit of study participation for all such participants includes an opportunity to provide brief advice on safe levels of drinking and the risks of intoxication.

2.2. Studies of craving in drug dependent individuals

More ethical challenges are raised by craving research on persons with an addictive disorder. A variety of factors can adversely affect these persons' ability to provide free and informed consent to participate in craving research. Participants should not be intoxicated or suffering from withdrawal when asked to consent (Carter & Hall, 2008). Standardised scales for assessing drug intoxication and withdrawal (Ebbets, 1994, Smith et al., 2006 and Wesson and Ling, 2003) should be used to assess the capacity of addicted individuals to give consent. The chronic use of addictive drugs can also cause significant cognitive deficits (e.g. Wernicke–Korsakoff syndrome) or serious psychiatric symptoms (e.g. psychosis, anxiety and depression) that may impair capacity to provide informed consent. Steps should be taken to identify impaired individuals when there is a reasonable expectation of such impairment, as is the case for any research that is likely to involve cognitively impaired individuals (e.g. persons with traumatic brain injury).

2.2.1. Administering addictive drugs and inducing craving

Some bioethicists have argued that addicted individuals, by definition, have impaired autonomy and so lack the capacity to provide free or internally uncoerced consent to participate in studies that involve administering addictive drugs (Charland, 2002 and Cohen, 2002). Similar issues are also raised by the provision of financial compensation for study participation that may serve as an inducement because the money may be used to purchase drugs (see Festinger et al., 2008, Festinger et al., 2005 and Fry et al., 2006).

We have argued elsewhere (Carter and Hall, 2008 and Carter and Hall, 2012) that the loss of autonomy in addicted persons is not as absolute as these bioethicists suggest. Addiction does not abrogate an individual's capacity to make autonomous decisions (Carter and Hall, 2008 and Levy, 2006) but it can impair autonomy in certain situations. For example, the emergence of strong cravings during recruitment could undermine an individual's ability to fully assess the consequences of research participation (Carter & Hall, 2008).

A common concern has been that participation in research that involves giving small doses of a participants' drug of dependence or presenting drug-related cues may increase subsequent drug use. Evidence from follow up studies suggests that research participation does not increase drug use nor produce relapse in abstinent addicted individuals (Bigelow et al., 1994, Faillace et al., 1972, Kranzler et al., 1990, Meyer, 2000 and Modell et al., 1993). Indeed, there is evidence that most addicted individuals who participate in such research derive some benefit from their participation (Montoya & Haertzen, 1994). At a minimum, they receive a medical examination by a health professional in a supportive environment. Ideally, they also receive information about and referral to treatment services, along with educational material about their drug of choice (Adler, 1995, Carter and Hall, 2008 and Fitzgerald and Hamilton, 1996).

The risks of participating in this type of research are also much lower than the risks run by addicted individuals in their everyday drug use (Adler, 1995). Non-abstinent addicted individuals, for example, typically use illicit drugs of unknown strength and purity, by the most hazardous route of administration (e.g. intravenous injection), often using poor injection techniques. In a research setting, by contrast, pharmaceutical drugs of known strength and purity are administered under medical supervision, at doses lower than those typically used recreationally, and medical care is àvailable to deal with adverse events (Adler, 1995, Dolinsky and Babor, 1997 and Montoya and Haertzen, 1994).

Similarly, it seems unlikely that the presentation of cues or events that may induce craving in a research setting will have much effect upon subsequent drug use. It can be difficult to elicit marked craving responses and addictive behaviour in laboratory settings (Meyer, 2000). The cravings induced in the laboratory may be measured using sensitive neuropsychological instruments, but such experiences are likely to be significantly less than cravings experienced in an addicted person's everyday living. This has not been demonstrated empirically and it would be difficult to do so.

The limited studies of the effects of research participation on addicted participants suggest that participants are certainly no worse off, and are often generally better off, than those that do not participate (Dolinsky and Babor, 1997 and Montoya and Haertzen, 1994). Therefore, in carefully conducted studies that take the precautions described above, it is ethically acceptable to provide addicted individuals with small, carefully controlled doses of their drug of dependence, or to present drug-related cues that aim to measure craving.

2.2.2. Studies of craving in formerly dependent individuals

The ethics of conducting craving research in formerly addicted individuals or those who are in treatment is a highly contested issue, with different bioethicists reaching very different conclusions. The National Bioethics Advisory Commission (1999) argued that only addicted individuals who were not in treatment should be allowed to participate in research studies in which drugs of dependence were given. They reasoned that giving abstinent persons a drug of addiction would increase the likelihood of their relapsing to drug use. A similar inference could also be made about research that used cues to induce craving.

By contrast, Cohen (2002) has argued that only addicted individuals who have entered treatment have the capacity to freely consent to participate in research that involves the administration of an addictive drug. He argued that addicted persons who enter treatment demonstrate that they are able to make autonomous and voluntary decisions about their drug use. Those who continue to use drugs are, on his view, "in denial" about their condition and so lack the insight to make autonomous decisions about participating in such a research study. Cohen provides no empirical evidence for either claim.

A decision to enter treatment does not guarantee that the individual possesses the volitional capacity to choose whether or not to participate in research. Many addicted individuals enter treatment as a result of coercion, whether from courts, friends or families, or employers (Pritchard et al., 2007 and Wild, 2006). An addicted individual who agrees to participate in a research study in the absence of external coercion is arguably making a more autonomous and internally uncoerced decision than someone entering treatment while in withdrawal or under legal duress.

2.2.3. Recruiting addicted participants and obtaining consent to craving studies
There are a number of ways that researchers can recruit addicted individuals for craving research studies in order to maximise the validity of their informed consent. First, situations that may elicit strong cravings for drugs should be avoided or mitigated. Researchers should avoid over-emphasising that drugs will be administered when recruiting study participants. They should also avoid administering drugs shortly after obtaining participants' consent (Walker, 2008). A participant's belief that a drug of addiction will be immediately administered may trigger strong cravings that overwhelm rational appraisal of the risks and benefits of study participation. As Meyer (2000) showed, the opportunity to consume a drug of addiction is necessary to elicit strong cravings in even the most severely dependent individuals, even in the presence of cues associated with drug use. The possibility of drug administration at some later time (e.g. in one or two weeks) is arguably much less likely to do so (Walker, 2008). However, such a requirement would place a significant burden upon researchers by reducing recruitment that may affect the ability to conduct research. Obtaining informal oral consent at recruitment prior to booking in the study session where formal consent is obtained may be sufficient. The need for such measures needs to be balanced against the risks and benefits of participation. Further research is needed to determine whether separating the process of consent from drug administration significantly reduces the potential for craving to interfere with consent and to establish what duration is best. Consent should also be obtained in locations that are free of triggers of craving, such as drug smells or paraphernalia.

Second, researchers could also obtain participants' consent in ways that minimise stress and cognitive load that may impair decision making (Baumeister, 2003 and Levy, 2006). This could be accomplished by using audio-visual tools, such as videos that clearly communicate the risks and benefits of participating in research (Dunn and Jeste, 2001 and Fureman et al., 1997). The validity of consent may also be increased by a consent process that assesses participants' understanding of the research study and the risks and benefits of participation, and corrects any misunderstandings (Festinger, Dugosh, Croft, Arabia, & Marlowe, 2010). More research is required on how best to obtain consent to research participation in substance abusing populations (Carter and Hall, 2008, Dunn and Jeste, 2001 and Festinger et al., 2010).

Third, consent may be facilitated by the use of clinical diagnostic tests (e.g. MacArthur Competence Assessment Tool or mental state assessment) to assess participants' capacity to consent (Smith et al., 2006). Diagnostic tools raise their own practical and ethical issues. Any diagnostic tool would need to be brief and easy to administer so to not impede research. The test would also need to be specific — it would be unethical to falsely exclude someone from research participation, particularly if participation was beneficial. There are a great number of factors, such as poor education, low intelligence or the presence of comorbid psychological disorders that can affect the ability of a specific addicted individual to provide free and informed consent to participate in craving studies. More research is needed to develop diagnostic instruments that will provide a better measure of a potential subject's ability to understand, comprehend and freely choose to participate in a research study.

3. Ethical issues in clinical trials of novel treatments to reduce craving

3.1. Pharmacological treatments of craving

A number of drugs are claimed to have "anti-craving" properties. These include: acamprosate, bupropion, disulfiram, modafinil and naltrexone (see O'Brien, 2005 and Yahyavi-Firouz-Abadi and See, 2009). There is some evidence from clinical trials that these drugs can reduce relapse in the short term but their effects on craving are less certain because craving has either not been measured or has been measured poorly (Connor et al., 2005 and Statham et al., 2011).

A concern is that the long term use of drugs that reduce craving may have adverse effects on motivation. It has been suggested, for example, that long term use of naltrexone may produce dysphoria and depressive symptoms (Dean et al., 2006 and Miotto et al., 2002) and reduce the rewarding effects of everyday activities such as eating (Yeomans & Gray, 2002), sex (Murphy, Checkley, Seckl, & Lightman, 1990) and physical exercise (Daniel, Martin, & Carter, 1992).

Some bioethicists have also been critical of using drugs that interfere with motivation or desires; they argue that these attributes are fundamental to our sense of self or identity (Kass, 2002). While the use of drugs in healthy adults that significantly alter our sense of self may raise important ethical concerns (Levy, 2007), the situation is arguably different when these drugs are used to treat addiction. Addiction is a condition that in itself adversely interferes with self, reduces life choices and causes significant emotional, physical and psychological harm to addicted individuals and their families. Addicted persons are already using drugs than can affect their personhood. Drugs that ameliorate these impairments would arguably enable rather than impair expression of

self. As long as addicted individuals are free to refuse anti-craving medications, the impact on personhood raises little ethical concern.

3.2. Pharmacologically-assisted cue extinction

The chronic use of addictive drugs impairs cue extinction, which may explain why the addition of cue-exposure treatment (Kantak & Nic Dhonnchadha, 2011) does not improve upon other psychotherapeutic treatments (Kavanagh et al., 2006). Kantak & Nic Dhonnchadha (2011) suggest that administering memory enhancing drugs such as D-cycloserine may improve extinction in cue-exposure treatment. These drugs aim to assist individuals to maintain abstinence by weakening the ability of cues to evoke strong cravings that may overcome a person's rational capacity to maintain abstinence (Sofuoglu, 2010). Small scale pilot studies of D-cycloserine have not found any significant clinical effects, although this might be explained by a lack of power to detect improvement (Kantak and Nic Dhonnchadha, 2011 and Kaplan et al., 2011). Should they prove effective, ethicists will no doubt raise concerns about the pharmacological manipulation of memory (Glannon, 2006). Such concerns, however, will need to be tempered by a pragmatic analysis of the often highly speculative effects of these drugs on memory compared to the significant adverse effects of continued addiction.

3.3. Neurosurgical treatment of drug craving: DBS and TMS

More radical, neurosurgical approaches have been used to treat craving-induced relapse to drug use. Neurosurgeons in Russia and China have destroyed the nucleus accumbens (Gao et al., 2003) and the cingulated gyrus (Gao et al., 2003 and Medvedev et al., 2003) to eliminate cravings or compulsions to use drugs. An outcry over the ethical unacceptability led to a ban on these procedures, although reports suggest a renewed interest in China (Xiao, 2011).

Deep brain stimulation (DBS) is a more reversible form of neurosurgery that is hoped will eliminate cravings and cure drug addiction (Krack et al., 2010, Lu et al., 2009, Luigjes et al., 2011 and Stelten et al., 2008). It involves inserting stimulating electrodes deep into the brain regions involved in addiction, such as the nucleus accumbens. There have been several case reports of the effects of DBS on addiction (see Carter, Bell, Racine, & Hall, 2010) that proponents believe reduces relapse to drug use by eliminating drug cravings (Kuhn et al., 2007, Kuhn et al., 2009, Kuhn et al., 2011 and Müller et al., 2009) and the motivation to use drugs (Rouaud et al., 2010 and Vassoler et al., 2008).

Given the history of psychosurgery, caution is required. While DBS is not as damaging as ablative neurosurgery, it does present risks and can result in permanent damage. The psychiatric side-effects of this novel treatment are largely unknown. For example, some patients with Parkinson's disease who have been treated with DBS have developed impulsive behaviours similar to addictive disorders (Frank et al., 2007 and Smeding et al., 2007). We discuss these ethical issues in greater detail elsewhere (Carter and Hall, 2011 and Carter et al., 2010).

Transcranial magnetic stimulation (TMS) is a non-invasive method of electromagnetically manipulating neural activity in the brain using a magnetic coil placed against the person's skull (Machii et al., 2006 and Pascual-Leone et al., 2002). TMS raises fewer health and safety concerns than neurosurgery or DBS because it does

not involve physical penetration of neural tissue (Anand & Hotson, 2002). Small scale TMS trials have reduced drug cravings in the laboratory, but these are yet to be replicated in larger trials or shown to produce clinically meaningful results (Camprodon et al., 2007 and Feil and Zangen, 2009). A TMS device received Food and Drug Administration approval for the treatment of major depression, but there remains significant doubts about its clinical utility in psychiatric disorders (Rosack, 2007), including addiction (Slotema, Blom, Hoek, & Sommer, 2010).

3.4. Psychotherapeutic treatments

Analyses of ethical issues in the treatment for craving often focus on trials of pharmacological approaches because of concerns about the adverse effects of drug treatments. Psychotherapeutic approaches may also have adverse effects for several reasons. First, evaluations of psychotherapies have usually only measured the benefits of participating in treatment; there have been few studies of their harmful effects, and these have been limited in scope (Berk & Parker, 2009). It has been estimated that 7–15% of patients treated for addiction are worse off following psychotherapy, as indicated by increased alcohol or other drug use, increased levels of anxiety and depression, or new encounters with the criminal justice system (Boisvert, 2010, Lilienfeld, 2007 and Moos, 2005). Studies suggest that certain forms of psychotherapy may be more harmful to particular individuals, although more research is needed to predict which individuals are likely to benefit from or be harmed by particular psychotherapies (Berk and Parker, 2009 and Lilienfeld, 2007).

4. Preventing craving-induced relapse: drug vaccines and sustained-release implants

A different approach to ameliorating the impact of cravings is to use long-acting medications that prevent craving-induced "slips" resulting in a return to chronic use. Such long-acting relapse interventions include drug vaccines and sustained-release implants. Drug vaccines block the psychoactive effects of a drug by stimulating the production of antibodies that bind to the target drug, preventing it from acting on receptors in the brain (Kosten and Owens, 2005 and Nutt and Lingford-Hughes, 2004). Sustained-release (SR) implants are formulations of orally administered anti-craving drugs (e.g. naltrexone, buprenorphine) that overcome the problem of poor compliance associated with short-acting medications. SR implants include depot injections (intramuscular injections of oil suspensions) and large polymer implants that steadily release a dose of the active drug (Krupitsky et al., 2011 and Ling et al., 2010).

Proponents argue that these treatments will prevent craving-induced slips from leading to a return to dependent drug use. For example, vaccination against nicotine could prevent a relapse to smoking in abstinent smokers during the first few months after quitting when cravings for cigarettes are greatest (Vocci & Chiang, 2001). While a nicotine vaccine could be circumvented by increasing the dose of nicotine, it is hoped that attenuating the rewarding effects of nicotine may be enough to prevent many from returning to daily smoking (Hall, 2002 and Vocci and Chiang, 2001).

Studies suggest that these approaches are not as effective as was hoped (Maastricht University Medical Center, 2009, Martell et al., 2009 and National Institute on Drug Abuse, 2010). Should more effective relapse prevention treatments be developed, a number of ethical issues will need to be considered in using them to treat addiction and protect against the consequences of craving. First, questions of consent may arise if

long-acting relapse prevention medications are used under legal coercion, such as when treatment is ordered by the criminal justice system. Addicted women, for example, could be compelled to undergo “vaccination” to protect a foetus from the effects of substance use.

Second, long-acting relapse preventions may prove counterproductive if addicted individuals can circumvent them by increasing drug dose, using more dangerous drugs, or more harmful routes of administration (e.g. intravenous injection) thereby increasing the risk of harm (e.g. cardiac arrest from cocaine use) (Murray, 2004). Some research suggests that this response to long-acting relapse preventions is likely (Degenhardt, Gibson, Mattick, & Hall, 2008).

Third, long-acting relapse interventions do not block cravings (Ashcroft & Franey, 2004). They will need to be used in conjunction with behavioural treatments and psychosocial support if abstinence is to be maintained (Nutt & Lingford-Hughes, 2004). None of these issues preclude the use of vaccines or implantable antagonists to treat addiction and reduce relapse. These are nonetheless important issues that should be examined in clinical trials.

5. Conclusions

In conducting research on craving, scientists and clinicians need to ensure that prospective participants have the capacity to understand and assess the risks and benefits of participating. Addicted individuals may be cognitively impaired, because of withdrawal symptoms, intoxication or comorbid psychiatric conditions, in ways that reduce their ability to understand the consequences of participating in research. Craving studies that provide addicted individuals with their drug of addiction may induce cravings that undermine a dependent individual's ability to consider the risks of participation. Researchers should attempt to: 1) identify potential participants who may be unable to provide free and informed consent to participate in research; 2) recruit participants in ways that facilitate or increase a subject's ability to provide meaningful consent; and 3) design experiments in ways that minimise any potential harms while maximising the possible benefit of participating.

Treatments that increase addicted individuals' ability to avoid or resist strong urges to use drugs may increase their chances of achieving enduring abstinence. Clinicians need to consider the risks and benefits of treatment and carefully communicate these to patients. The effectiveness and safety of emerging treatments, whether psychological, pharmacological or a combination of the two, should be assessed by randomised controlled clinical trials.

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