SMOKING KILLS (ALCOHOLICS)? SHOULDN'T WE DO SOMETHING ABOUT IT?

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Abstract — In general, 'drinkers smoke', and a high proportion of the alcohol-dependent population is also nicotine-dependent. Statistically, the majority of alcoholics will die of smoking-related, rather than alcohol-related, disease. This co-dependent subpopulation may have higher levels of nicotine dependence, and find smoking cessation more difficult. Major reasons are that concurrent alcohol use, and/or prior alcohol exposure, may change the reinforcing effects of nicotine, and that each drug becomes a pharmacological cue for the expectation of the other. If so, then smokers whose nicotine dependence is impacted by alcohol, represent a large and distinct sub-population in which both the therapeutic and molecular targets for smoking cessation are altered. This, in turn, has implications for the validity of animal models of nicotine reinforcement, and for the development of novel smoking cessation medications. It is no longer possible to ignore the fact that the two most prevalent and damaging addictive drugs in our society are very commonly used by the same individuals. Without a better understanding of the psychological and pharmacological interactions between alcohol and nicotine that impact dependence, we cannot hope to provide appropriate medications for this large and problematic patient group. Our intention in this opinion overview is to use the current literature to provide a framework for future studies into the impact of alcohol use on the reinforcing effects of nicotine.

CONTRIBUTION OF SMOKING TO MORBIDITY ASSOCIATED WITH ALCOHOL DEPENDENCE

In the alcohol dependent population, smoking is commonly estimated in excess of 80% (Bobo, 1992; Miller and Gold, 1998) and it is estimated that smokers have a significantly increased risk (between 4 and 10%) for developing alcohol use disorders (see DiFranza and Guerrera, 1990; Grant et al., 2004). This 'co-dependence' has a major effect on morbidity because there are many diseases, including several cancers (Sasco et al., 2004), as well as cardiovascular disease, in which smoking is the major risk factor (Benowitz, 2003), and in which the use of alcohol provides added risk. Indeed, because of the prevalence of smoking-related morbidity, alcoholics are more likely to die of smoking-related disease rather than directly from alcohol-related medical disorder (see, Hurt et al., 1996; Hurt and Patten, 2003). Given this situation, it is essential to address both dependencies when they co-exist. This overview and opinion paper considers whether this population of 'alcoholic smokers' should be considered as distinct from 'smokers' in relation to treatment for their nicotine dependence. However, there is an additional factor to be considered, because this focus on adult prevalence neglects other ways in which alcohol exposure or use during development might alter nicotine addiction. For example, there is a strong relationship between use of alcohol in early adolescence and prevalence of smoking in adulthood (Paavola et al., 2004). Similarly, fetal alcohol exposure via maternal drinking is reported to be associated with an increased incidence of drug abuse including nicotine dependence in adulthood (Yates et al., 1998; Obot et al., 2001). Of course, these are merely associations, and common genetic or environmental factors that predispose to drug use in general almost certainly contribute. However, this does not invalidate the hypothesis that chronic alcohol use, and/or developmental exposure to alcohol, impacts nicotine dependence, and there is ample evidence for this (see below). Effective medications that target 'interactive' risk could have a significant impact on morbidity in both the alcohol dependent, and the nicotine dependent, populations.

This paper is not intended as a traditional review of the literature regarding the pharmacological or behavioral overlap between nicotine and alcohol dependence. Rather, it is to draw attention to some of the complexities that are involved and to discuss issues which merit further study. These issues range from concerns of shared etiologies, differential trajectories (including gene/environment interactions) and under-studied issues such as individual differences in pharmacokinetic/dynamics and pharmacogenetics. It is hoped that this will help emphasize the need for molecular, pharmacological and behavioral studies of risk, prevention, intervention and treatment for this population.

DOES ALCOHOL USE OR EXPOSURE CREATE A DIFFERENT KIND OF SMOKER?

If the co-incidence of smoking and drinking in adults were the result of a common predisposition to drug dependence, it should affect the smoking and drinking populations equally. However, this relation is asymmetric. Why this is the case is not certain but may be explained, in part, due to differential rates of these behaviors/disorders. It is estimated that ∼>80% of individuals with a diagnosis of alcohol dependence also smoke heavily (DiFranza and Guerrera, 1990; Bobo, 1992). In contrast, although the risk of alcohol use disorders is increased among heavy smokers, the estimated prevalence is only about ∼40% (DiFranza and Guerrera, 1990; Grant et al., 2004). Mathematically, this pattern suggests that individuals who continue to use alcohol in adulthood are significantly more likely to continue to smoke than...
those who do not. This is supported directly by findings showing that adults who also use alcohol have higher levels of nicotine dependence (Marks et al., 1997; Horn et al., 2000; Hughes et al., 2000; John et al., 2003; Hettling et al., 2005) and report greater difficulty in quitting smoking (DiFranza and Guerrera, 1990; Novy et al., 2001). In alcohol dependent individuals in treatment, the severity of nicotine dependence is associated with greater alcohol craving (Hillemacher et al., 2006) and these characteristics can also extend to individuals who were heavy drinkers, but who have become abstinent (Junghanns et al., 2000; Currie et al., 2001; John et al., 2003). Thus, based on prevalence in adults, the potential impact of prior or concurrent alcohol use on nicotine dependence must be in excess of 40% of the total smoking population.

Turning once again to developmental factors, the relationships between developmental alcohol exposure and adult nicotine dependence remain after controlling for potential genetic and environmental confounds. For example, the effects of fetal alcohol exposure on adult nicotine and drug dependence were observed in adopted-away offspring, and remained even when the characteristics of the biological parents were factored out (Yates et al., 1998). The findings therefore suggest that exposure of the developing CNS to alcohol may increase susceptibility to nicotine dependence. This is strongly supported by studies in which early postnatal chronic exposure of rats to ethanol resulted in a marked increase in the reinforcing properties of nicotine in adolescence (Rogers et al., 2004). In humans, it is difficult to assess the relative importance of fetal, adolescent and adult exposure, because developmental alcohol exposure also increases the use of alcohol in the adult (Novy et al., 2001; John et al., 2003). However, moderate drinking in pregnancy remains at about 10% (Office of Applied Studies, 2004), and adolescent experimentation with alcohol is common (O’Malley et al., 1998), thus, it is very likely that all of these periods of exposure are important. In summary, nicotine addiction is directly or indirectly influenced by alcohol use for at least 40% of the nicotine addicted population. If alcohol use alters therapeutic targets for smoking cessation (see below) then this sub-population has to be considered separately in deciding treatment options, and in the development of new medications. Furthermore, if nicotine exposure increases risk for alcohol craving and/or use, it may be important to reduce exposure directly and/or the smoking-related cues among alcoholics initiating recovery. However, concluding that ALL nicotine use/exposure is negative may be premature; particularly in light of data suggesting that acute nicotine administration may have a differential impact (improve) cognitive performance in alcoholics compared to non-alcoholic smokers, at least early in recovery (Ceballos et al., 2005, 2006).

**IMPACT OF ALCOHOL USE ON REINFORCING EFFECTS OF NICOTINE**

Although psychosocial, environmental and genetic reasons are important in the incidence of co-dependence on alcohol and nicotine, the development of appropriate treatments specifically requires an understanding of the pharmacological interactions between reinforcing effects of these drugs. The key mechanisms by which alcohol use affects development, exposure, modifies the reinforcing effects of nicotine. First, concurrent use of alcohol with nicotine (in which both drugs are present in the brain at the same time) is very common, and some reasons may be pharmacological and impact reinforcement. For example, the stimulant effects of nicotine may offset some of the ‘aversive’ acute CNS depressant effects of alcohol (Schafer and Michael, 1992). There is also evidence that the more permanent cognitive deficits associated with chronic alcohol use can be reversed by nicotine administration (Meyerhoff et al., 2006) making the cognition-enhancing effects of nicotine potentially more reinforcing than they would be in non-alcoholic smokers. However, not all use of nicotine is co-incident with alcohol use, even in individuals who use the drugs ‘concurrently’, and the temporal pattern may influence the reinforcement obtained. For example, anxiety, and hyperalgesia occur during an alcohol hangover (McKinney and Coyle, 2006), and cigarettes smoked before drinking resumes may relieve this negative effect by virtue of the ‘secondary’ pharmacological actions of nicotine (which include anxiolysis and potent analgesia) (Bromi et al., 1993). Similar negative effects occur during alcohol withdrawal, and it is a common observation that smoking escalates during attempts to quit alcohol. It is possible that cigarette smoking serves as a ‘substitute reinforcer’ during periods of alcohol abstinence (see Bickel et al., 1995 for discussion) but this is likely an oversimplification. For example, Mello and colleagues (Mello et al., 1980) found that cigarette smoking served as a complementary reinforcer, with cigarette smoking decreasing as alcohol intake decreased. Similarly, Rosenson and colleagues (Rosenson et al., 1997) found that in recovering male alcoholics, exposure to alcohol cues resulted in significantly increased urge to drink, and urge to smoke (although smoking itself did not increase).

Additionally, although we often do not understand the mechanisms, chronic alcohol use may be associated with psychiatric illness that impacts the reinforcement provided by nicotine. For example, major depression is commonly associated with alcohol dependence (Modesto-Lowe and Kranzler, 1999) and may make the mood-elevating effects of nicotine more salient. Clinical depression is certainly also a major negative factor in attempts at smoking cessation (Glassman et al., 2001; Burgess et al., 2002; Blaock et al., 2006) and this might make a treatment with antidepressant properties, such as bupropion, particularly effective in this significant sub-population (‘depressed alcoholic smokers’) (Hayford et al., 1999; Tonstad, 2002). These limited examples illustrate a general principle, individuals who smoke and drink may obtain different reinforcing effects of nicotine from those who do not also use alcohol. If so, the therapeutic targets for smoking cessation in this sub-population are also likely to be different.

To move from purely ‘pharmacological’ considerations, classical conditioning is recognized as playing a major role in the addictive properties of cigarette smoking, and concurrent use of alcohol and nicotine may make each become a ‘cue’ for the expectation of the other. Thus, smoking cessation may be confounded by ‘craving’ for nicotine initiated by use of alcohol (Gulliver et al., 1995; Field et al., 2005) but
the relation is complex. As above, some theories predict that nicotine use should be increased during alcohol deprivation (Tiffany, 1990) whereas others suggest a less reciprocal relationship (Rohsenow et al., 1997). Whatever theoretical model is applied, there is little argument that the role of such pharmacologically and behaviorally conditioned stimuli is potentially great and may be prolonged, particularly when conditioning occurs in periods of CNS plasticity, such as during adolescence (Sullivan and Rudnik-Levin, 2001). Once again this shifts the important therapeutic target, in this case toward blunting pharmacological conditioning.

IMPACT OF DEVELOPMENTAL ALCOHOL EXPOSURE ON REINFORCING EFFECTS OF NICOTINE

Adolescent and fetal drug exposure can impact behavior and mood throughout life. For example, fetal alcohol exposure (via maternal use), or heavy use in adolescence, influence attention, pain sensation, and anxiety in adulthood and are also strong risk factors for adult nicotine addiction (e.g. Hill et al., 2000; Hellstrom-Lindahl and Nordberg, 2002; Adriani et al., 2003; Novak et al., 2003). Once again, alcohol exposure might modify the reinforcing effects of nicotine. For example, attention deficit hyperactivity disorder (ADHD) is commonly associated with fetal alcohol exposure (Mattson and Riley, 1998). ADHD is also strongly associated with adolescent nicotine use (Sullivan and Rudnik-Levin, 2001) which might reflect a form of ‘self-medication’ in which attentional effects of nicotine are specifically reinforcing (see Upadhyaya, 2006). Other types of reinforcement may also achieve higher salience. In animal studies, early postnatal exposure of rat pups to alcohol produces a hyperalgesia that extends into adolescence. Nicotine is now a more effective analgesic, and has greater reinforcing properties in this group than in adolescent controls (Rogers et al., 2004). We hypothesize that ‘developmental exposure’ to alcohol may change the strength and character of subsequent reinforcing properties of nicotine. If so, then alcohol use in adolescence, and/or exposure in utero, may impact nicotine addiction, even in smokers who do not currently use alcohol.

THERAPEUTIC TARGETS AND MODELS FOR MEDICATIONS DEVELOPMENT

These theoretical considerations of interactions between reinforcing effects of alcohol and nicotine suggest two types of novel therapeutic target. One is a partial substitution for alcohol by nicotine during periods in which alcohol is negatively reinforcing, and the other is cross-conditioning between alcohol and nicotine. The first suggests that some potentially reinforcing effects of nicotine (stimulation, analgesia, anxiety, attention) may acquire greater value during concurrent use of, or following developmental exposure to, alcohol. Currently these therapeutic targets are almost ignored in the development of smoking cessation therapy. Thus, in most animal models that are used for medication development, the focus is on ‘positive reinforcement’ in otherwise untreated laboratory animals. Under these conditions, nicotine acts as a ‘very weak positive reinforcer’, for example, unlike cocaine, amphetamines and opiates, it does not induce strong conditioned place preference (CPP) (Fudala and Iwamoto, 1986; Iwamoto, 1990; Shoaib et al., 1994). This does not reflect the strength of nicotine dependence in humans (regardless of alcohol use), and casts some doubt on the face and predictive validity of the models. If the reinforcing properties of nicotine in humans include the ‘secondary’ pharmacological actions of nicotine, then it would improve face validity if animal screens could be developed to reflect this. One way to do this would be to include alcohol treatment in the models. Thus, as described above, alcohol exposure to neonatal rats both induces hyperalgesia, and markedly increases nicotine-induced CPP in adolescence (Rogers et al., 2004). Consequently, a case could be made for adding developmental alcohol exposure to animal screens for medications for nicotine addiction. Whether this would improve the predictive validity of such screens and models remains to be seen! It certainly would improve the face validity for the large proportion of potential patients who use alcohol and nicotine together. However, not only are the therapeutic targets of reinforcement and conditioning shifted in this sub-population, the molecular targets may also be altered.

IMPACT OF ALCOHOL USE ON PRIMARY MOLECULAR MECHANISMS OF NICOTINE REINFORCEMENT

The positive reinforcing effects of nicotine are primarily mediated by brain nicotinic acetylcholine receptors (nicAChRs). Nicotine has a high affinity specifically for nicAChRs of the alpha4/beta2 subtype, and the diversity of effects of nicotine is partly because alpha4/beta2 nicAChRs are widespread in the brain, and sub-serve several functions. However, the brain concentrations of nicotine achieved in smokers are about two orders of magnitude greater than the affinity for alpha4/beta2 nicAChRs (Brody et al., 2006), thus activating several other nicAChR subtypes. Indeed, the high affinity of nicotine for alpha4/beta2 receptors may desensitize this entire subtype population in the brain during smoking, making agonist properties of nicotine in smoking more pronounced on nicAChRs other than the alpha4/beta2 subtype (Brody et al., 2006)! These other receptor subtypes are also differentially involved in the behavioral functions of the cholinergic nervous system in the brain. Once again, these many pharmacological actions may acquire more reinforcing ‘value’ in different mood or physiological states, or when other drugs are present, or during withdrawal from drugs (including nicotine itself). As above, if after alcohol exposure, nicotine analgesia acquires reinforcing value, then a subtype-specific nicAChR ligand with greater (or more prolonged) analgesic properties may be a more effective ‘substitute’. Additionally, if alcohol exposure ‘up-regulates’ a specific subtype of nicAChR, then ligands selective for this subtype may be more effective in this sub-population. Since alcohol and nicotine both acutely affect alpha4/beta2 subunit-containing nicAChRs (e.g. Owens et al., 2003) chronic use of either drug might modify the nicAChR population, producing a
major effect on the reinforcing effects of nicotine. For alcohol, the evidence for this is abundant, but confusing (Booker and Collins, 1997; Coverton and Connolly, 1997; Marszalec et al., 1999), with increases and decreases in nicAChRs in different brain areas, under different conditions. Of most relevance here, there has been surprisingly little research on the effects of chronic alcohol exposure on nicAChR subtype density in those brain areas believed to mediate reinforcing effects of nicotine. Conversely, chronic nicotine exposure has been repeatedly shown to up-regulate alpha4/beta2 nicAChRs (Paut et al., 1996), but we were unable to find any research on the combined effects of alcohol and nicotine exposure on the density of nicAChR subtypes in different brain areas. This kind of information seems essential if smoking cessation medications are to be effectively targeted on the co-dependent population.

IMPACT OF ALCOHOL ON SECONDARY MOLECULAR MECHANISMS OF NICOTINE REINFORCEMENT

In common with all drugs of dependence, the positive reinforcing effects of nicotine are believed to be mediated by enhanced effects of dopamine (DA) released in the nucleus accumbens from neurons originating in the ventral tegmental area (VTA) (Liu et al., 2006). In the case of nicotine, DA release in the accumbens is partly mediated by nicotine-induced presynaptic glutamate release acting on N-methyl-D-aspartate receptors (NMDARs) (Kosowski et al., 2004). Further, both alcohol and nicotine dependence are associated with marked elevations in circulating homocysteine, a potent NMDAR antagonist (Jacques et al., 2001; Bleich et al., 2005). In consequence, long-term effects of alcohol and nicotine on NMDARs have implications for the reinforcing effects of nicotine. Thus, chronic alcohol treatment during development or in adulthood, can alter NMDAR numbers, and/or function, and/or subunit expression (e.g. Lovingier, 1996; Tsai, 1998; Hoffman 2003). The potential for pharmacological interactions between alcohol and nicotine at this molecular target is high, because chronic nicotine exposure may have similar effects to alcohol on NMDARs (Trujillol and Akil, 1995). Despite these remarkable coincident effects of alcohol and nicotine on glutamate neurotransmission, very little research has focused on effects of either, or both, drugs on alterations in glutamate receptors in the brain regions that subserve reinforcement. Since the same receptors are also involved in classical conditioning (see below) any such alterations take on even greater significance as molecular therapeutic targets. In addition to glutamate, the opioid transmitter system also regulates the dopaminergic neurons from the VTA to the nucleus accumbens. In the case of positive reinforcement caused by alcohol there is little doubt that release of endogenous opioids plays a role (and this probably underlies the efficacy of the opioid antagonist, naltrexone, in relapse). For nicotine, the situation is much less clear. There is evidence that opioid antagonists can reduce nicotine reinforcement (Brauer et al., 1999; Almeida et al., 2004; Rukstalis et al., 2005) and some analgesic effects of nicotine are also sensitive to opioid antagonists (Simons et al., 2005). Both findings suggest that nicotine causes release of endogenous opioids (Olive et al., 2001), but an alternative possibility is that some opioid agonists inhibit some nicAChRs (Almeida et al., 2004). Regardless of whether nicotine directly affects the opioid system, alcohol-induced alterations in opioid receptor numbers and distribution might have a general effect on reinforcing mechanisms that would impact those of nicotine. If so, opioid receptor antagonists might have a therapeutic role in co-dependence as well as in alcohol dependence (see below).

MOLECULAR TARGETS FOR SMOKING CESSATION

Nicotinic receptors (nicAChRs)

As above, there are several potentially reinforcing effects of nicotine involving different nicAChR subtypes. Which subtypes might be specifically involved in reinforcement in patients whose nicotine use is impacted by alcohol use or exposure is largely unknown. As regards medications development, one can say only that alcohol use, or prior exposure, may alter the therapeutic targets (i.e. the reinforcing effects of nicotine) and that these targets are likely related to different populations of molecular targets (i.e. nicAChR subtypes). Currently these subtleties are ignored. Thus nicotine dependence is usually treated with nicotine itself (via a more slowly absorbed, less toxic, route than smoking) or bupropion (an antidepressant with nicAChR antagonist properties). Given the complexities inherent in nicAChR desensitization, and the pharmacokinetics of nicotine during smoking, it is uncertain whether the efficacy of these treatments in smoking cessation is due to nicotine antagonism, or substitution. However, for medications development this does not matter—novel ligands for the nicAChR might be efficacious by either or both of these mechanisms. What we need in order to answer these questions is a battery of subtype-selective nicAChR agonists and antagonists that can be assessed for their ability to inhibit different aspects of nicotine dependence. For example, recent evidence from alpha7-nicAChR ‘knock-out’ mice suggests strongly that this receptor subtype is crucially implicated in the nicotine physical withdrawal syndrome (Grabus et al., 2005). However, without highly selective alpha7-ligands, this cannot be confirmed pharmacologically, and cannot inform a medication development program. To target nicAChRs for smoking cessation in alcohol dependent patients we need to know which receptor subtypes are responsible for which aspect of nicotine dependence, we need to know how these subtypes are altered by alcohol exposure, and we need the right pharmacological tools to evaluate therapeutic potential. Currently we have none of these!

Glutamate receptors

Another molecular target for smoking cessation is suggested by the perceived importance of pharmacological conditioning in relapse mechanisms involving co-dependence. Classical conditioning, including cue-induced relapse, is generally believed to involve glutamate transmission in the extended amygdala (Weiss and Koob, 2001; Littleton and Ziegglansberger, 2003), with a final impact on reinforcement via glutamate terminals in the nucleus accumbens (Saulskaya and others).
Soloviova, 2004). The major receptors involved in extreme forms of conditioning, such as ‘conditioned fear’, are glutamate/NMDARs (Biala and Kotilinska, 1999), although evidence is accumulating that metabotropic glutamate receptors (e.g. mGluR5s) are also involved (Lin et al., 2005; Lominae et al., 2006), perhaps via positive modulation of NMDARs (Pisani et al., 2001; Marino and Conn, 2002). This makes the NMDAR (and mGluR5s) a potential therapeutic target, both for the prevention of acquisition of dependence, and for prevention of relapse when this is induced by cues associated with prior drug use. However, the role of NMDARs in conditioning reflects important physiological functions in learning and memory, making these receptors a problematic molecular therapeutic target. Nevertheless, ‘inhibitory modulators’ of the NMDAR, such as the natural product agmatine, reduce expression of pathological conditioning without adversely affecting learning and memory (Papp et al., 2002) and also inhibit drug self-administration in animals (Bisaga et al., 2000). Also, in contrast to antagonists such as ketamine, these ‘NMDAR modulators’ are reportedly without abuse potential. Inhibitory modulators of NMDARs are therefore of potential value in reducing the impact of alcohol-conditioned cues on nicotine dependence. The anti-relapse drug acamprosate is believed to act as an indirect inhibitor of NMDAR function (Littleton and Zieglgansberger, 2003; De Witte et al., 2005) and is suggested to suppress both protracted alcohol withdrawal, and alcohol-conditioned responses that precipitate relapse (Cole et al., 2000; McGeehan and Olive 2003). Therefore, if either alcohol withdrawal, or alcohol-conditioned responses, play a role in maintaining nicotine use, then agents like acamprosate should be of value for smoking cessation in this patient group. Because alcohol exposure changes NMDAR numbers and composition (see above) the effects of NMDAR modulators on any kind of cue-induced reinstatement of nicotine self-administration may also be altered in this population. We surmise that it is these changes that may provide the best potential molecular targets for treatment of co-dependence. This possibility has never been tested.

Opioid receptors

In addition to acamprosate (above) the only other current generally-approved treatments for alcohol dependence are disulfiram and naltrexone. The mechanism of disulfiram is not predicted to impact smoking, however, since some evidence implicates the endogenous opioid system in reinforcing effects of nicotine, it is logical to consider the effect of naltrexone. The evidence is mixed. Naltrexone has been reported to have no beneficial effect on smoking cessation (Sutherland et al., 1995; Wong et al., 1999) or sometimes to have a small positive effect when combined with the nicotine patch (Krishnan-Sarin et al., 2003; O’Malley et al., 2006). Two studies have found this effect only in females (Epstein and King, 2004; Byars et al., 2005; King et al., 2006). Naltrexone has also been reported to blunt the effect of smoking cues during treatment with the nicotine patch (Hutchison et al., 1999). As regards the effect of naltrexone on smoking behavior when used as a treatment for alcohol dependence, one study showed a rather small effect in the direction of reduced cigarette use (Rohsenow et al., 2003). On balance, opioid receptors cannot be excluded as a potential therapeutic target for smoking cessation in alcohol dependent individuals, but the currently available opioid antagonists seem not to be very effective.

SUMMARY AND CONCLUSIONS

A major sub-group of the nicotine-addicted population, perhaps the majority, is affected by prior alcohol exposure, or current alcohol use. Despite this, most medications development ignores this possibility, and indeed there is very little basic research into the interactions between the reinforcing effects of these two most common drugs of dependence. Traditionally the argument has been that we do not know enough about reinforcing mechanisms of either drug to begin to study them together. However, this is no longer the case, and we submit that one cannot understand the reinforcing effects of either drug in humans UNLESS one considers them together! This review suggests that the sub-population of smokers who are also alcohol dependent requires special consideration because the strength and character of nicotine addiction may be altered. Successful treatment of their alcohol dependence is highly desirable, but this is a hollow victory if the abstinent alcoholic then dies of smoking-related disease. Smoking does kill alcohols, and it is certainly about time that we tried to do something about it!

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