Rational treatment of addiction

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Treatment of alcohol and drug addictions, which has been neglected medically for a long time, is currently sparked with optimism. Craving for alcohol can be treated with two newly registered drugs: naltrexone and acamprosate. New approaches to symptom relief during detoxification or during maintenance therapies are rationally based on experimental and clinical work. It is now clear that addictive drugs are surrogates of natural substances involved in the 'reward system'.

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Abbreviations

5HT	5-hydroxytryptamine
GABA	γ-aminobutyric acid
NMDA	*N*-methyl-D-aspartate
SSRI	selective serotonin re-uptake inhibitors
VTA	ventral tegmental area

Introduction

Drug dependence has a major impact on society, economically and socially. The dimensions of illegal drug use have called for drastic measures in order to reduce their availability, without much success. The implementation of tougher drug laws also seems to have little preventive effect, but has increased the costs for law enforcement. Faced with the situation that we may be losing 'the war on drugs', the current debate focuses on 'harm reduction'. A contributing factor to this change in focus has been the spread of HIV and hepatitis by shared needles among addict populations. Medications that keep the addict from the street, such as methadone tablets for the heroin addict, are accepted medically and legally. Besides reducing the exposure to infective agents, this drug has the added advantage of legality and puts an end to antisocial behavior. Thus, harm is reduced for the individual and for society. It is beyond the scope of this review to analyze the current debate on harm reduction, which should be separated from the issue of legalization. Certainly, to care for the individual who is already an addict is a medical problem, and a difficult one [1].

In the public eye drug dependence equals illegal drug use; however, consequences of dependence on tobacco (nicotine) and alcohol, which are legally available (with certain restrictions), are considerable. Numerous studies have shown that tobacco smoke is a major environmental health hazard. The medical consequences of heavy drinking of alcohol are more difficult to estimate, as self-reports of consumption are unreliable. It has been estimated, however, that about 30% of beds in medical services may serve people who have alcohol-related medical problems (RD Moore *et al.*; see Note added in proof). On a quantitative basis, and considering medical complications only, there is no doubt that tobacco and alcohol are the dominating problem drugs. This review focuses on the developments in understanding of addiction as a medical concern and as a biological phenomenon, and also on the recent addition of new drug therapies.

The public attitude

There is probably no other medical area that has been influenced so much by the public attitude as drug dependence. A moral stand that 'they brought it on themselves' [2] certainly influences therapists and the public alike. In fact, alcoholism itself has sometimes not been considered a medical problem as such, only its consequences. Medical treatment has been concentrated on somatic complications whereas the root to these problems, excessive drinking, has been left to counsellors, or recovered alcoholics in organizations such as Alcoholics Anonymous. The possibility of medical intervention for alcoholism, however, was recognized by a few scientists, and led to the introduction of the drug disulfiram.

Disulfiram

The discovery of disulfiram is an illustrative and amusing study of accidental discoveries in pharmacology, not only of a new drug, but also of a new treatment principle. During the Second World War, Erik Jacobsen and Jens Hald, working in occupied Denmark, were searching for substances to kill scabies (vermicides). Disulfiram was tried because it binds copper and it was thought that lower species had a stronger need for this metal. Successful animal experiments seemed to prove the principle. When Jacobsen and Hald tried the substance on themselves they 'developed a peculiar hypersensitivity to alcoholic drinks, very much like an acute allergic reaction' with flushes, pulse acceleration, nausea and vomiting [3]. The mechanism for disulfiram action was discovered by injecting alcohol into a subject and sensing the smell of acetaldehyde on the breath [4]. It would take several years to find a clinical use of disulfiram, because it was thought there would not be enough patients to treat!

Disulfiram has been found to be a very safe drug, with minimum toxicity except when alcohol is consumed. It has been widely used, particularly in the early post-detoxification period. It is definitely not a cure and several alcohol treatment centers use it restrictively. In a position paper by the American College of Physicians [5] it was concluded that disulfiram can be an effective

adjuvant in the compliant patient. There is little evidence, however, that the long term outcome on alcoholism is affected. Another enzyme inhibitor is daidzin, the active principle in the Chinese herbal medicine Kudzu, which has been used for the treatment of alcoholism for centuries. Daidzin reduces voluntary alcohol intake in experimental animals and acts by blocking mitochondrial aldehyde dehydrogenase [6].

The 'reward center'

Why do certain substances, which are chemically unrelated and which interact differently with different types of receptors, induce dependence? Although this question cannot be answered in a simple straightforward manner, certain general characteristics are common, the most important being an interaction with reward mechanisms. Classic experiments have identified a particular brain nucleus, the nucleus accumbens, as critical for self-stimulation. Rats with electrodes implanted into this region of the brain were found to happily press a bar that activated a current. Other spontaneous behavior was compromised and the self-stimulating animal lost body weight and neglected grooming and tidiness. Other areas that are important for reward include the ventral tegmental area (VTA), which feeds into the nucleus accumbens, and the frontal cortex, which receives projections from the accumbens. These nuclei and adjacent structures including the amygdala, are often alluded to as the 'reward center'—clearly an artificial concept, but convenient to use [7].

A central role is also played by the mesolimbic dopamine pathway, which projects from the VTA to the nucleus accumbens. The most powerful drugs of abuse, amphetamine, cocaine and heroin, act directly on these pathways. Amphetamine and cocaine inhibit dopamine re-uptake into the nerve terminals in the nucleus accumbens, thereby potentiating the actions of dopamine. The interaction occurs at the level of the dopamine-transporter, which is responsible for re-uptake of dopamine in the synapse. Consequently, mice in which the dopamine-transporter has been knocked out are spontaneously hyperactive and are unresponsive to amphetamine or cocaine (which cause hyperactivity in the wild type animal) [8]. Surprisingly, however, mice that lack the transporter will self-administer cocaine [9]. Heroin interacts with this dopamine pathway by disinhibiting inhibitory interneurons in the VTA, thereby increasing the activity in dopamine neurones. Heroin also acts directly in the nucleus accumbens. Direct supporting evidence has been obtained by microdialysis, a technique that allows the measurement of neurotransmitters in the extracellular fluid at the site of release [10]. Recent work has also shown that nicotine and cannabinoids (the active ingredient in cannabis) increase dopamine levels by an action on enkephalinergic neurones that, by release of opioid peptides, disinhibit the inhibitory influence on dopaminergic cell bodies [11]. These results have added to the general significance of the mesolimbic dopamine pathway for drug dependence and have also been used as arguments that nicotine and cannabinoids are dependence-producing substances.

A generalized model for the actions of dependence-producing drugs is, of course, attractive. It is becoming more common to find individuals who take several drugs, or drugs and excessive alcohol—for example, smokers are 10 times more likely to become alcoholics than nonsmokers [12].

Drugs of abuse as surrogates of natural reward substances

Certain endogenous systems were discovered on the basis of the actions of drugs of abuse. The now classic example is the opioid peptide system. Prototype opiates such as morphine and meperidine act almost exclusively through the μ opioid receptor. Mice with a μ receptor knockout do not become morphine-dependent [13]. As well as the μ receptor, two other receptors, the δ and κ receptors, have been defined. The opioid peptides also derive from three genes encoding for preproenkephalin, preprodynorphin and preproopiomelanocortin. Each of these genes is polyfunctional (i.e. several biologically active peptides may be generated by selective proteolytic processing with proteases). Enkephalins act on the μ receptor and also on the δ receptor with an equal or higher affinity. β-endorphin, which is a 32 amino acid peptide derived from proopiomelanocortin, also acts on both receptors. Both enkephalins and β-endorphin are self-administered when provided exogenously to the nucleus accumbens or VTA in a similar way as heroin or morphine [14]. Thus a number of attempts have been made to analyze the potential influence of exogenous (chronic) opiate administration on the activity in endogenous opioid systems. Opioid mechanisms in alcohol addiction have recently come into focus, with the clinical use of naltrexone to prevent relapse in alcoholism (see below).

The dynorphin peptides primarily act on the κ receptor and are pharmacologically very distinct from the opiates or enkephalins and β-endorphin. Behaviorally, these substances are not self-administered and there is evidence that dynorphin peptides microinjected into the nucleus accumbens reduce the release of dopamine from the terminals of mesolimbic nerve endings [15]. It may be speculated that dynorphin peptides are endogenous modulators of the reward system. In fact, strains of rats that are comparatively resistant to developing dependence express higher dynorphin levels in the nucleus accumbens [16]. Substances acting on κ receptors may become interesting in the control of drug-induced reward [17].

The discovery of the cannabinoid-1 (CB1) receptor, which is almost unique to the brain [18], and the identification of endogenous substances acting on the CB1 receptor, is also intriguing. The first isolated substance showing

affinity for the CB1 receptor was anandamide, generically related to arachidonic acid, but otherwise structurally unique [19]. Anandamide and other related substances are probably active in the absence of external stimuli [20]. It is, however, questionable whether they are truly addictive or not: levonantradol, a synthetic agent that acts on the CB1 receptor, has shown limited clinical use as an antiemetic in cancer patients. The issue of dependence has not been a major concern [21]. Animal studies with cannabinoid antagonists that have very recently become available may challenge this contention. In rats continuously infused with the major active ingredient in cannabis, Δ^9-tetrahydrocannabinol, the cannabinoid antagonist SR 141716A precipitates withdrawal [22].

Drug dependence and craving

Drug dependence may be considered an altered state, a change in homeostasis certainly involving several neurotransmitters. Dependence can be manifested physiologically in the abstinence reaction, which can be medically significant (in the case of alcohol) or extremely unpleasant (in the case of heroin). These phenomena can be readily reproduced in experimental animals. In fact, substitution of a withdrawal reaction is a common test situation for studying the abuse potential of a new drug. A very important component is the psychological dependence and the conditioning to a stimulus that might be associated with the use of a drug, such as a syringe for the intravenous abuser, or the liquor store or a favorite bar for the alcoholic. Principally, an addict could relapse for two different reasons. First, the addict experiences withdrawal with painful symptoms, which can appear weeks or months after discontinued drug intake. Such periods of protracted withdrawal may be very critical times in an addict's life. Second, there is the longing for euphoria or detachment from reality, or 'craving'. The term is meaningful to the patient, because it gives a name to the strong desire to continue with the abuse, despite the consequences. Animal models designed on the basis of self-stimulation procedures have been developed to predict clinical efficacy of pharmacotherapies for drug abuse [23].

Drug treatment during abstinence

Attempts to provide pharmacotherapies to alcohol and drug addicts have previously focused on different aspects of the clinical manifestations of abstinence. Hyperactivity in excitatory systems, primarily the glutamate system, is a characteristic feature of alcohol withdrawal, and may require pharmacological treatment using benzodiazepines or symptom-oriented therapies. The guiding principle is to protect the brain from potentially hazardous excitatory influence in the acute phase of abstinence and not long term rehabilitation. This important area of treatment, which is not the focus here, has been reviewed recently [24]. Hyperactivity during alcohol and drug withdrawal is also apparent in the noradrenergic systems. Electrophysiological recordings from the locus ceruleus, the major source of noradrenergic innervation of the cerebral cortex, indicate hyperactivity long after drugs have been discontinued and it has been thought that this could be a driving force in drug-seeking behavior [25]. The α-adrenergic stimulant clonidine, used clinically to treat hypertension, has been used to treat addicts. Clonidine reduces the severity of abstinence reactions according to the hypothesis and makes the patient more comfortable. Clonidine is used quite widely to relieve abstinence reactions, which suggests that the drug has a therapeutic niche. Controlled studies have not indicated a major usefulness of the drug in the long term, however.

To reduce discomfort, but also to affect long term prognosis, heroin addicts undergoing detoxification have been given the opiate antagonist naloxone in a continuous infusion, under general anaesthesia, for several hours. This approach, which has received some publicity, requires intensive care facilities that necessarily limit its practical use. Only a few medical centers are currently using this technique. So far, the published case material is rather small and, given the large variability in treatment outcome, it will take time to evaluate the clinical efficacy of the procedure [26,27].

Drug abstinence as a depressive state

The detoxified addict is in a vulnerable state. Co-morbidity with depressive symptoms is quite common. A number of trials using antidepressive drugs to treat alcoholics and drug addicts have been reported. A potential confounding variable is in the selection of patients, particularly in the extent to which patients show symptoms of depressive co-morbidity.

The literature regarding the therapeutic use of antidepressants in drug dependence is inconclusive. Patients with depressive symptomatology who respond to therapy may be less motivated to continue antidepressant use as a consequence of the antidepressive effect. A recent study on imipramine demonstrated efficacy in opiate addicts with depressive disorders [28]. The patients also reported less consumption of opiates or alcohol, but very few produced opiate-free urines. Imipramine is a monoamine re-uptake inhibitor that mainly acts on the serotonin (or 5-hydroxytryptamine, 5HT) transporter. It is not ideal for mechanistic studies because its main metabolite, desmethylimipramine, acts primarily on the noradrenaline transporter. Currently, selective serotonin re-uptake inhibitors (SSRIs) have a broad use in depression and personality disorders. Interestingly, studies in animal models show that agents acting on the serotonin system affect alcohol intake.

Several recent studies have used the SSRI fluoxetine. Grabrowski *et al.* [29] studied over 200 cocaine addicts who, besides receiving fluoxetine treatment, participated in individual psychotherapy sessions. Cocaine use persisted in all groups and fluoxetine was ineffective in

reducing drug use. Another study [30] using a relatively small number of alcoholics also failed to demonstrate a clinical effect of the drug, although patients reported less alcohol craving. A positive therapeutic outcome was recorded by Janiri *et al.* [31] in alcohol-dependent patients, however; this effect may lead to fluoxetine being used to treat alcoholics rather than cocaine addiction.

Another SSRI, citalopram, was used [32] in mildly to moderately dependent alcoholics. No other treatment was given. There was an early effect, but no significant effect could be seen after three months of treatment.

The $5HT_2$ antagonist, ritanserin, showed some promise in animal models of alcohol and drug dependence. The clinical evaluation has been less conclusive, however. Naranjo *et al.* [33] investigated ritanserin under double-blind conditions in heavy alcohol drinkers who were not seeking treatment. They were asked to rate their mood, desire to drink and degree of intoxication. Ritanserin did not seem to have a major effect on alcohol intake, although the subjects reported increased intoxication and fatigue in experimental drinking sessions. A multicenter study of ritanserin in over 400 alcohol-dependent subjects over a 12 week period with a double-blind cross-over design has recently been reported [34]. The subjects also received behavioral therapy. Although the patients showed marked clinical improvement, there were no significant differences in alcohol drinking or clinical outcome with ritanserin therapy. In a placebo-controlled study [35], cocaine addicts were subjected to cues that precipitated reproducible changes in skin temperature, heart rate and skin resistance, indicative of high craving. Ritanserin had no effect, except on skin temperature, thereby failing to confirm a significant effect on cue-induced craving.

The partial 5HT agonist *m*-chlorophenylpiperazine (*m*-CPP) was studied in recently detoxified alcoholics in a placebo-controlled design. The patients reported a better mood and a decreased craving for alcohol [36]. *m*-CPP has also been tested experimentally in alcoholics and control subjects using positron emission tomography (PET). Brain glucose utilization was elevated in the nucleus accumbens, the head of the caudate nucleus and orbital cortices; however, in alcoholics, the response was blunted, suggesting that a serotonin challenge is much less active [37].

Buspirone, an anxiety-reducing drug that acts on the 5HT system, has been studied clinically, producing mixed results. A recent meta-analysis [38] indicates that the drug is effective on some of the psychopathology observed in detoxified alcoholics but probably has no effect on alcohol drinking per se.

The drugs described above were introduced as antidepressants and not for alcohol or drug abuse. Extrapolation has not proven entirely successful, except in subjects with a depressive co-morbidity. It has been pointed out that there may be technical reasons that limit the power of extrapolation from existing indications to new ones [33].

Opiate agonist/antagonists

Methadone

In the early post-war era, the epidemic spread of intravenous heroin use, and the associated increasing number of deaths by overdose and infectious diseases, prompted Dole and co-workers (see Note added in proof) to investigate the long-acting and orally active substance methadone as a heroin substitute. This treatment successfully took addicts off the streets, improved their personal and social lives and reduced mortality. The treatment is accepted by most patients and may continue for many years. Withdrawal from methadone is less dramatic than from other opiates, but more prolonged. Because methadone is no cure for opiate addiction it will not be discussed here in more detail. In most countries it is reserved for chronic cases, which means that many potential subjects may acquire hazardous diseases or die before treatment is initiated.

Naltrexone

The narcotic antagonist naltrexone is practically a pure antagonist that effectively blocks all opiate actions and protects the addict from narcotics in case he relapses. It is orally active, has a long duration and binds with high affinity to the μ opioid receptor, the same receptor that is activated by morphine-like opiates. The use of naltrexone in opiate addiction is, however, very limited because of lack of patient compliance; only for the highly motivated patient could this be a drug of choice. Attempts have been made to produce slow-release or otherwise long-acting preparations, which are practical as naltrexone is very potent. Even compulsory naltrexone depot injections have been considered.

A more successful extended use of a medication for a new indication is the use of naltrexone in the treatment of alcoholism. Animal studies (M Kornet, C Goosen and JM van Ree; see Note added in proof) indicated that alcohol releases opioid peptides, and that opiate antagonists suppressed voluntary drinking; however, the significance of this phenomenon was unclear. The potential usefulness of naltrexone stems from the subjective report by a few patients who were being treated for heroin use and had less liking for alcohol. Two reports published back-to-back [39,40] indicated a substantial reduction in alcohol intake in those patients taking naltrexone. The effect was particularly marked if the drug treatment was combined with psychotherapy. Further work indicated that naltrexone took away the 'high' feeling [41]—a slip into drinking would therefore not have the same consequences. The literature on naltrexone treatment in alcoholism is already quite extensive and the area has been subjected to several reviews (CP O'Brien, LA Volpicelli and JR Volpicelli; see Note added in proof).

From a mechanistic point of view, it is interesting that the best responders have higher levels of craving [42]. The reduction of alcohol-induced craving by naltrexone suggests that opioid peptides are centrally involved. As data accumulate it is possible that subgroups of alcoholics likely to respond to naltrexone will be identified.

Buprenorphine

An alternative to the pure antagonist is buprenorphine, a very long-acting analgesic. Buprenorphine has a rather complex pharmacology. Data indicate that it is a partial agonist at μ receptors and an antagonist at κ receptors. Because buprenorphine requires only infrequent dosing it is practical for use in addicts. The substance is liked by addicts because it apparently retains some euphorigenic properties. An early study by Jasinski *et al.* [43] indicated buprenorphine's usefulness as an opiate agonist/antagonist. Mello and Mendelson [44] found that buprenorphine suppressed self-administration of heroin under controlled conditions in a research ward. In both studies the termination of buprenorphine did not produce significant withdrawal reactions. This may be a consequence of the weak effect at μ receptors and also the effect of blocking endogenous opioids acting on κ receptors. More recent studies compared the effects of methadone and buprenorphine on patients using street heroin [45,46]. Patients seemed to do equally well on a low dose of methadone and on buprenorphine, whereas a higher dose of methadone gave better results. An intriguing observation was made: buprenorphine suppresses cocaine self-administration [47], suggesting that cocaine releases opioid peptides that act in the 'reward center'. As concurrent use of heroin and cocaine is common, buprenorphine treatment seems attractive; however, in the studies cited [46,47], opiate use declined but cocaine use did not, and the clinical effectiveness of buprenorphine in cocaine addiction remains to be proven.

Non-opiates

Acamprosate is the calcium salt of *N*-acetyl-homotaurine; it may be considered a structural analogue of the neurotransmitter γ-aminobutyric acid (GABA) and it probably interacts with GABA receptors. The main site of action, however, is in the glutamate transmitter system and the *N*-methyl-D-aspartate (NMDA) receptor [48], which is developmentally and functionally coupled to the $GABA_A$ receptor (Y Ben-Ari *et al.*; see Note added in proof). The action of acamprosate is probably activity-dependent. Since ethanol also interacts with GABA and NMDA receptors, and hyperexcitability of NMDA receptors is a characteristic of the withdrawal syndrome, there is a direct link to chronic alcohol use. The most significant effects may be blockade of neuronal hyperexcitability and reduction of calcium fluxes. In animal models of alcohol craving, acamprosate is able to reduce alcohol intake [49•] and block the increased alcohol intake imposed by abstinence [50].

Acamprosate has been studied clinically for several years [51]. It reduces relapse in the post-detoxification period and is well tolerated. It is not active as an antidepressant or general anxiolytic. A more recent study [52] describes a double-blind placebo-controlled study of detoxified alcoholics who received acamprosate for 48 weeks and who were then observed for an additional 48 weeks. Patients who received acamprosate did statistically better during the treatment period and had a lower drop-out rate. They also did better during the follow-up observation period. In conclusion, acamprosate is well tolerated and has shown clinical efficacy in controlled studies. It is now a registered drug (Campral®, Merck, Darmstadt, Germany) for treatment of alcoholism in several European countries.

Conclusions

Addiction, and prevention of relapse especially, are becoming areas for specific pharmacotherapy. It is now being realized that craving for alcohol or drugs is a unique state that is central to the long-term prognosis. Agents that reduce craving, or possibly other physiological reactions in the detoxified patient, can be a helpful adjunct to psychotherapy or other forms of supportive therapy. As such, the area is new and two drugs, naltrexone and acamprosate, were registered during the past few years specifically for those indications. It has been pointed out that adequate therapy of addiction requires a long term commitment. In that sense it is similar to diseases such as adult-onset diabetes or hypertension, which are also related to lifestyle, smoking, ingestion of a diet with high levels of cholesterol and sugar, and so on, and which develop gradually in those who are genetically disposed. As in these diseases, a successful therapeutic result requires a change in behavioral attitudes [2•].

The successful introduction of drugs for a new indication may attract interest from drug companies, who may develop other, perhaps more efficacious, substances. Basic research in this field now gives a solid foundation at both a fundamental molecular and cellular level [53] and at a systems level [54•]. The failure to self-regulate alcohol intake or to stop taking various drugs may be studied in several animal models, specifically addressing not only the clinically important issue of craving, but also the issue of relapse and the importance of conditions for further drug use. Environmental factors such as stress can also be investigated. The number of potential neurotransmitter systems and circuits that characterize 'hedonic homeostasis dysregulation' [54•] is staggering. There are also nonhuman primate models of addiction. Quite interestingly, among monkeys living in troops under field conditions, individuals have been observed that show characteristic behavior and are inclined to select alcohol rather than water for drinking, in contrast to most individuals [55]. The analogy to human behavior is clear.

In clinical research, new technologies are available that have so far had very little application in studies of

addiction. It is well known that there are genetic disposition factors for developing alcoholism. So far, investigations into the genetic basis for the disposition are in their infancy. It is likely from animal studies that several genes, perhaps interacting, are relevant [56•]. Studies are in progress to identify candidate gene in the amino acid, dopamine, 5HT and opioid systems. A potentially powerful approach would be to test a particular therapy in a population of patients characterized with respect to relevant target genes. So far, only modest attempts have been made using this approach.

The rapid development of brain imaging techniques offers excellent possibilities for the study of craving. Application of such methodology will be particularly relevant in the evaluation of potential anti-craving substances. Recent examples of the application of PET [37] or functional magnetic resonance imaging [57] are illustrative. These techniques can provide quantitative information on otherwise subjective phenomena.

Note added in proof

The work cited as (RD Moore *et al.*; Dole and co-workers, M Kornet, C Goosen and JM van Ree, CP O'Brien, LA Volpicelli and JR Volpicelli and Y Ben-Ari *et al.*; see Note added in proof) have now been published [58–62].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interst
- •• of outstanding interest

1. Nadelmann EA: **Commonsense drug policy.** *Foreign Affairs* 1998, **77**:111-126.
2. O'Brien CP, McLellan AT: **Myths about the treatment of addiction.** *Lancet* 1996, **347**:237-240.
3. Jacobsen E: **Accidental discoveries in pharmacology.** In *Proceedings of the Sixth International Congress on Pharmacological Drug Therapy: 1975 July 20–25; Helsinki.* Edited by Tuomisito J, Paasonen MK. Oxford: Pergamon Press; 1975:3-15.
4. Hald J, Jacobsen E, Larsen V: **The sensitizing effect of tetraethylthiuram disulphide (Antabuse) to ethylalcohol.** *Acta Pharmacol* 1948, **4**:285-296.
5. American College of Physicians: **Disulfiram treatment of alcoholism.** *Ann Int Med* 1989, **111**:943-945.
6. Keung WM, Vallee BL: **Kudzu root: an ancient Chinese source of modern antidipsotropic agents.** *Phytochemistry* 1997, **47**:499-506.
7. Koob GF, Bloom FE: **Cellular and molecular mechanisms of drug dependence.** *Science* 1988, **242**:715-723.
8. Giros B, Jaber M, Jones SR, Wightman RM, Caron MG: **Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter.** *Nature* 1996, **379**:606-612.
9. Rocha BA: **Cocaine self-administration in dopamine-transmitter knockout mice.** *Nat Neurosci* 1998, **1**:132-137.
10. Ungerstedt U, Herrera-Marschitz M, Jungnelius U, Ståhle L, Tossman U, Zetterstrom T: **Dopamine synaptic mechanisms reflected in studies combining behavioural recordings and brain dialysis.** *Adv Biosci* 1982, **37**:219-231.
11. Pontieri FE, Tanda G, Orzi F, Di Chiara G: **Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs.** *Nature* 1996, **382**:255-257.
12. Hurt RD, Eberman KM, Croghan IT, Offord KP, Davis LJ Jr, Morse RM, Palmen MA, Bruce BK: **Nicotine dependence treatment during inpatient treatment for other addictions: a prospective intervention trial.** *Alcohol Clin Exp Res* 1994, **18**:867-872.
13. Matthes HW, Maldonado R, Simonin F, Valverde O, Slowe S, Kitchen I, Befort K, Dierich A, Le Meur M, Dolle P, Tzavara E *et al.*: **Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the μ-opioid-receptor gene.** *Nature* 1996, **383**:819-823.
14. Van Ree JM: **Endorphins and experimental addiction.** *Alcohol* 1996, **13**:25-30.
15. Spanagel R, Herz A, Shippenberg TS: **Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway.** *Proc Natl Acad Sci USA* 1992, **89**:2046-2050.
16. Nylander I, Hyytia P, Forsander O, Terenius L: **Differences between alcohol-preferring (AA) and alcohol-avoiding (ANA) rats in the prodynorphin and proenkephalin systems.** *Alcohol Clin Exp Res* 1994, **18**:1272-1279.
17. Kuzmin AV, Semenova S, Gerrits MA, Zvartau EE, Van Ree JM: **Kappa-opioid receptor agonist U50,488H modulates cocaine and morphine self-administration in drug-naive rats and mice.** *Eur J Pharmacol* 1997, **321**:265-271.
18. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC: **Cannabinoid receptor localization in brain.** *Proc Natl Acad Sci USA* 1990, **87**:1932-1936.
19. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R: **Isolation and structure of a brain constituent that binds to the cannabinoid receptor.** *Science* 1992, **258**:1946-1949.
20. Richardson JD, Aanonsen L, Hargreaves KM: **SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice.** *Eur J Pharmacol* 1997, **319**:R3-R4.
21. Stambaugh JE Jr, McAdams J, Vreeland F: **Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis.** *J Clin Pharmacol* 1984, **24**:480-485.
22. Aceto MD, Scates SM, Lowe JA, Martin BR: **Dependence on delta 9-tetrahydrocannabinol: studies on precipitated and abrupt withdrawal.** *J Pharmacol Exp Ther* 1996, **278**:1290-1295.
23. Mello NK, Negus SS: **Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures.** *Neuropsychopharmacology* 1996, **14**:375-424.
24. Mayo-Smith MF: **Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American society of addiction medicine working group on pharmacological management of alcohol withdrawal.** *JAMA* 1997, **278**:144-151.
25. Rasmussen K: **Afferent effects on locus coeruleus in opiate withdrawal.** *Prog Brain Res* 1991, **88**:207-216.
26. Loimer N, Hofmann P, Chaudhry H: **Ultrashort noninvasive opiate detoxification.** *Am J Psychiatry* 1993, **150**:839.
27. Legarda JJ, Gossop M: **A 24-h inpatient detoxification treatment for heroin addicts: a preliminary investigation.** *Drug Alcohol Depend* 1994, **35**:91-93.
28. Nunes EV, Quitkin FM, Donovan SJ, Deliyannides D, Ocepek-Welikson K, Koenig T, Brady R, McGrath PJ, Woody G: **Imipramine treatment of opiate-dependent patients with depressive disorders. A placebo-controlled trial.** *Arch Gen Psychiatry* 1998, **55**:153-160.
29. Grabowski J, Rhoades H, Elk R, Schmitz J, Davis C, Creson D, Kirby K: **Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials.** *J Clin Psychopharm* 1995, **15**:163-174.
30. Kabel DI, Petty F: **A placebo-controlled, double-blind study of fluoxetine in severe alcohol dependence: adjunctive pharmacotherapy during and after inpatient treatment.** *Alcohol Clin Exp Res* 1996, **20**:780-784.
31. Janiri L, Gobbi G, Mannelli P, Pozzi G, Serretti A, Tempesta E: **Effects of fluoxetine at antidepressant doses on short-term**

outcome of detoxified alcoholics. *Int Clin Psychopharm* 1996, **11**:109-117.

32. Naranjo CA, Bremner KE, Lanctot KL: **Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems.** *Addiction* 1995, **90**:87-99.

33. Naranjo CA, Bremner KE, Poulos CX: **Research strategies to assess pharmacotherapies for alcoholism.** *Prog Neuro-Psychopharm Biol Psych* 1996, **20**:543-559.

34. Johnson B, Jasinski D, Galloway G, Kranzler H, Weinreib R, Anton R, Mason B, Bohn M, Pettinati H, Rawson R, Clyde C: **Ritanserin in the treatment of alcoholism.** *Psychopharmacology* 1996, **128**:206-215.

35. Ehrman RN, Robbins SJ, Cornish JW, Childress AR, O'Brien CP: **Failure of ritanserin to block cocaine cue reactivity in humans.** *Drug Alcohol Depend* 1996, **42**:167-174.

36. Buydens-Branchey L, Branchey M, Fergeson P, Hudson J, McKernin C: **Hormonal, psychological, and alcohol craving changes after m-chlorophenylpiperazine administration in alcoholics.** *Alcohol Clin Exp Res* 1997, **21**:220-226.

37. Hommer D, Andreasen P, Rio D, Williams W, Ruttimann U, Momenan R, Zametkin A, Rawlings R, Linnoila M: **Effects of m-chlorophenylpiperazine on regional brain glucose utilization: a positron emission tomographic comparison of alcoholic and control subjects.** *J Neurosci* 1997, **17**:2796-2806.

38. Malec TS, Malec EA, Dongier M: **Efficacy of buspirone in alcohol dependence: a review.** *Alcohol Clin Exp Res* 1996, **20**:853-858.

39. Volpicelli JR, Alterman AI, Hayashida M, O'Brien C: **Naltrexone in the treatment of alcohol dependence.** *Arch Gen Psychiatry* 1992, **49**:876-880.

40. O'Malley S, Jaffe A, Chang G, Schottenfeld R, Meyer R, Rounsaville B: **Naltrexone and coping skills therapy for alcohol dependence. A controlled study.** *Arch Gen Psychiatry* 1992: 881-887.

41. Volpicelli JR, Watson NT, King AC, Sherman CE, O'Brien CP: **Effect of naltrexone on alcohol "high" in alcoholics.** *Am J Psychiatry* 1995, **152**:613-615.

42. Jaffe AJ, Rounsaville B, Chang G, Schottenfeld RS, Meyer RE, O'Malley SS: **Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient treatment matching.** *J Consult Clin Psychol* 1996, **64**:1044-1053.

43. Jasinski DR, Pevnick JS, Griffith JD: **Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction.** *Arch Gen Psychiatry* 1978, **35**:501-516.

44. Mello NK, Mendelson JH: **Buprenorphine suppresses heroin use by heroin addicts.** *Science* 1980, **207**:657-659.

45. Strain EC, Stitzer ML, Liebson IA, Bigelow GE: **Comparison of buprenorphine and methadone in the treatment of opioid dependence.** *Am J Psychiatry* 1994, **151**:1025-1030.

46. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR: **Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse [see comments].** *Arch Gen Psychiatry* 1997, **54**:713-720.

47. Mello NK, Mendelson JH, Bree MP, Lukas SE: **Buprenorphine suppresses cocaine self-administration by rhesus monkeys.** *Science* 1989, **245**:859-862.

48. Madamba SG, Schweitzer P, Zieglgansberger W, Siggins GR: **Acamprosate (calcium acetylhomotaurinate) enhances the N-methyl-D-aspartate component of excitatory neurotransmission in rat hippocampal CA1 neurons *in vitro*.** *Alcohol Clin Exp Res* 1996, **20**:651-658.

49. • Spanagel R, Zieglgansberger W: **Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes.** *Trends Pharmacol Sci* 1997, **18**:54-59.

This is an authoritative review that focuses on the complex electrophysiology of acamprosate.

50. Heyser CJ, Schulteis G, Durbin P, Koob GF: **Chronic acamprosate eliminates the alcohol deprivation effect while having limited effects on baseline responding for ethanol in rats.** *Neuropsychopharmacology* 1998, **18**:125-133.

51. Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, Parot P, Ladure P, Libert C, Boismare F *et al.*: **Acamprosate appears to decrease alcohol intake in weaned alcoholics.** *Alcohol Alcohol* 1990, **25**:613-622.

52. Sass H, Soyka M, Mann K, Zieglgansberger W: **Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence.** *Arch Gen Psychiatry* 1996, **53**:673-680. [Erratum appears in *Arch Gen Psychiatry* 1996, **53**:1097.]

53. Nestler EJ, Aghajanian GK: **Molecular and cellular basis of addiction.** *Science* 1997, **278**:58-63.

54. • Koob GF, Le Moal M: **Drug abuse: hedonic homeostatic dysregulation.** *Science* 1997, **278**:52-58.

This paper describes an ambitious synthesis of behavioral correlates and neurobiological characteristics of drug dependence in rodent models.

55. Higley JD, Linnoila M: **A nonhuman primate model of excessive alcohol intake. Personality and neurobiological parallels of type I- and type II-like alcoholism.** *Rec Dev Alcohol* 1997, **13**:191-219.

56. • Buck KJ, Metten P, Belknap JK, Crabbe JC: **Quantitative trait loci involved in genetic predisposition to acute alcohol withdrawal in mice.** *J Neurosci* 1997, **17**:3946-3955.

An experimental study indicating that genetic disposition to alcohol sensitivity is polygenic. Human genetic studies are in their infancy. Initial claims that certain candidate genes segregate with alcoholism have not been confirmed.

57. Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP *et al.*: **Acute effects of cocaine on human brain activity and emotion.** *Neuron* 1997, **19**:591-611.

58. Moore RD, Bone LR, Geller G, Mamon JA, Stokes EJ, Levine DM: **Prevalence, detection and treatment of alcoholism in hospitalized parients.** *JAMA* 1989, **261**:403-407.

59. Dole VP, Nyswander ME: **Medical treatment for diacetylmorphine (heroin) addiction.** *JAMA* 1965, **193**:80-84.

60. Kornet M, Goosen C, van Ree JM: **Opioid modulation of alcohol intake in monkeys by low doses of naltrexone and morphine.** *Ann NY Acad Sci* 1992, **654**:469-471.

61. O'Brien CP, Volpicelli LA, Volpicello JR: **Naltrexone in the treatment of alcoholism: a clinical review.** *Alcohol* 1996, **13**:35-39.

62. Ben-Ari Y, Khazipov R, Leinekugel X, Caillard O, Gaiarsa J: **$GABA_A$, NMDA and AMPA receptors: a developmentally regulated 'ménage a trois'.** *Trends Neurosci* 1997, **20**:523-529.