Pharmacological means of reducing human drug dependence: a selective and narrative review of the clinical literature

Shih-Ku Lin^{1,2}

¹Department of Psychiatry, Taipei City Hospital and Psychiatric Center, Taipei and ²Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan

Correspondence

Dr Shih-Ku Lin MD, Department of Psychiatry, Taipei City Hospital and Psychiatric Centre, 309 SongDe Road, Taipei 110, Taiwan.
Tel.: +8862 2726 3141
Fax: +8862 2728 5059
E-mail: sklin@tpech.gov.tw

Keywords

addiction, anticraving, craving, drug dependence

Received

27 June 2012

Accepted

28 April 2013

Accepted Article

Published Online

23 May 2013

Substance abuse or addictive disorder is a global problem. A greater understanding of the associated changes in brain pathophysiology supports the notion that pharmacological treatments are part of the necessary treatment options. Craving is a core symptom of addictive disorder. It refers to a strong desire to use drugs again either to re-experience positive effects or to diminish negative experiences. Currently there are a number of medicines that are effective in the treatment of addictive disorders. These medications can either be for substitution (same pharmacological effect as the abused substance) or anticraving (decrease the craving of the abused substance). In this MEDLINE based review, specific compounds (naltrexone, acamprosate, topiramate, disulfiram, baclofen, N-acetylcysteine and bupropion) were selected that are known to diminish desire to use (anticraving effect) and that have been trialled for a number of different substance addictive disorders. Their therapeutic potential in clinical practice is discussed in light of their efficacy.

Introduction

In general, the term 'addiction' is used to refer to any behaviour that is out of control in some way. People often describe themselves as being addicted, for example, to a TV show or to clothes shopping. Historically, addiction in psychiatry has been regarded as a disorder that has physical and psychological dependence on psychoactive substances (for example alcohol, tobacco, heroin, cocaine and other drugs). The prevalence of addiction has increased markedly for recreational substances such as alcohol and nicotine and illicit drugs such as marijuana, amphetamine, cocaine and opioids. Internet addiction and pathological gambling are also problems found in most countries.

A short definition of addiction proposed by the American Society of Addiction Medicine [1] states that addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Addiction is characterized by an inability to abstain consistently, impairment in behavioural control, craving, diminished recognition of signifi-

cant problems with one's behaviours and interpersonal relationships, and a dysfunctional emotional response. For a broader definition, addiction is not necessarily limited to substance use, and it can include behaviour addictions such as internet [2], eating [3], gambling [4] and sex [5]. Craving is the core symptom of addiction. In general use, craving can occur across a dimension from a very weak desire (urge) to very strong desire to use substances or do something [6]. In clinical practice, craving usually refers to a strong desire or intense urge for some particular thing that one has previously experienced. Patients with substance dependence always have this symptom, and loss of control over substance use is considered a hallmark of addiction and is critical in relapse [7]. The ICD-10 diagnostic criteria of dependence syndrome refers to craving as a strong desire or sense of compulsion to take the substance [8]. In the Diagnostic and Statistical Manual of Mental Disorders [9], 'positive' craving is not included in the criteria due to it being the psychological momentum of an individual that is not easily measured in quantity or observed from

external observations. Rather, the criteria 'substance is taken to relieve or avoid withdrawal symptoms' can be regarded as 'negative craving'.

When addicted patients stop using a substance, places, people, actions and sensations associated with past drug use and their collection as episodic memories thus represent conditioned cues that trigger drug craving as a conditioned response [10]. Craving shares some common characteristics with obsession/compulsion in terms of ruminative thinking and repeated behaviour. An individual may be obsessive/compulsive to relieve an anxious mood, or take drugs to relieve the craving. However, the common pathway is to satisfy the reward system [11, 12].

Measurement of craving

Since craving is an internal psychological momentum, it is not easily measured by laboratory examinations or external observations. Hence, the degree of craving is usually reported subjectively and can be measured in different aspects for predicting relapse or intervention effects. One commonly used tool of assessing craving is the single item Likert type or visual analogue scale (VAS). When responding to a VAS, respondents specify their level of craving from none to extreme on a 100 mm line. There are also a lot of multiple item questionnaires and Rosenber [13] has reviewed a series of published rating scales regarding the subjective experience of craving to different substances. The author concluded that these self-report questionnaires were correlated significantly with the single item scale. Recently, biological indicators have been reported such as plasma concentrations of stress hormone [14] and brain-derived neurotrophic factor for the severity of withdrawal symptoms [15] or craving [16, 17]. However, further investigation and validation of these findings are required [18].

Definition of anticraving

As with antidepressant or antipsychotic medication, an anticraving medication has positive effects on craving, either by reducing the degree or counteracting the suffering of craving. In a review article, O'Brien [19] proposed that anticraving medication is possibly a new class of psychoactive medication. According to his broad definition, any medication that shows an effect for the prevention of relapse can be regarded as anticraving. In this context, it also includes the medication used in replacement therapy and substitution therapy, such as a nicotine patch or gum for nicotine dependence, or methadone for heroin dependence. However, from a pharmacological point of view, the function of an anticraving medication is to decrease or ameliorate the 'craving' rather than to supply

the 'craving agent'. Therefore, I have focused on the medications that have shown anticraving properties in this review.

Anticraving and reward system

Almost all abused drugs increase dopamine release in the mesolimbic pathway, which is crucial in the cascade reaction of the brain reward system [20]. This burst response depends on the activation and plasticity of glutamatergic *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors located on dopamine neurons [21, 22]. The mesopontine rostromedial tegmental nucleus (RMTg) is a recently discovered brain structure which is thought to influence profoundly reward-related pathways [23]. The RMTg is prominently GABAergic, receives dense projections from the lateral habenula and projects strongly to the midbrain ventral tegmental area and substantia nigra compacta [24]. Drugs of abuse can hijack synaptic plasticity mechanisms in key brain circuits, and reversing or preventing these drug-induced synaptic modifications may prove beneficial in the treatment of addiction disorders [25]. Most compounds showing an anticraving effect possess the ability to alternate or modulate the reward system.

Method

In this review, the author has selected specific compounds with anticraving characteristics that have been used in trials in human subjects regarding different substances (alcohol, nicotine, cocaine, opiates, amphetamines and cannabis) or behavioural (internet, gambling, binge eating/obesity) addictive disorders using the MEDLINE database, and categorized them into four levels: (i) positive effect by double-blind controlled trials, (ii) positive effect by open trials or case series reports, (iii) controversial effect and (iv) negative effect (Table 1).

Naltrexone

Naltrexone and its active metabolite 6- β -naltrexol are competitive antagonists at μ - and κ -opioid receptors, and to a lesser extent at δ -opioid receptors. Naltrexone was developed to treat opioid dependence because of its effect of blocking the euphoric effects of opioids [26, 27]. In a meta-analysis of 26 randomized controlled trials (RCTs) [28], the author concluded that oral naltrexone appeared to have some limited benefits in helping formerly opioid-dependent individuals to remain abstinent, although the quality of the evidence was relatively poor and heterogeneous. Naltrexone has been reported to have a lack of patient adherence and low treatment retention, and is only suggested as a second line medication after methadone or buprenorphine for opioid dependence by the World

Table 1

Anticraving effect on substance and other addictions

	Alcohol	Nicotine	Opioids	Cocaine	Amphetamine	Cannabis	Internet addiction	Pathological gambling	Binge eating/obesity
Naltrexone	++	±	++	±	+	–	+	++	+
Acamprosate	++	0	0	–	0	0	0	–	±
Topiramate	++	±	0	+	±	0	0	0	++
Disulfiram	++	0	0	++	0	0	0	+	0
Baclofen	+	+	±	–	0	–	0	0	0
N-acetylcysteine	0	±	0	+	0	+	0	+	0
Bupropion	0	++	0	–	±	–	0	±	+

++: positive effect by double-blind controlled trials; +: positive effect by open trials or case series reports; ±: controversial effect; –: negative effect; 0: no trial reported; *: combine with bupropion.

Federation of Societies of Biological Psychiatry [29]. The NICE guideline recommends naltrexone as a treatment option for people who have been opioid dependent but who have stopped using opioids, and who are highly motivated to stay free from the drugs in an abstinence programme. Naltrexone has a craving reduction effect on heroin [30, 31], while in other contexts of substance use, naltrexone has also shown an anticraving effect.

Naltrexone has been given to patients with alcoholism due to its effect of altering ethanol self-administration in animal studies, after the observation that alcohol activates the endogenous opioid system [32, 33]. Two separate randomized blind placebo-controlled trials [34, 35] demonstrated the efficacy of naltrexone on alcohol dependence, and it was licensed to treat this disorder in North America and Europe. Subsequently an animal study [36] demonstrated that the suppression of ethanol-reinforced behaviour by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine concentrations in the nucleus accumbens. Taken together, this evidence suggests that naltrexone modulates the reward system by blocking opioid receptors to produce an anticraving effect. Although there were two subsequent negative clinical trials [37, 38], trajectory-based re-analyses by the same group did support that naltrexone may have a clinically meaningful effect for alcohol dependent patients with a high chance of consistent drinking, even in studies where it failed to show efficacy in planned analyses [39]. Since naltrexone does not show any drug–drug interaction effect with ethanol or its metabolism, the phenomenon of decreasing the amount of alcohol drinking with naltrexone can be attributed to an ‘anticraving’ effect. Naltrexone can therefore be regarded as a prototype of anticraving medication. For another opioid antagonist nalmefene, early studies did not show efficacy on alcoholism [40, 41], although the latter RCT showed it was significantly better than a placebo in reducing heavy drinking days, very heavy drinking days, drinks per drinking day and in increasing abstinent days [42].

There is only one RCT on naltrexone with regards to cocaine dependence [43]. The results showed no significant effect of treatment on time to first cocaine-positive urine or craving, and only some effect on less cocaine use over time. When trialled on dual dependences of cocaine and alcohol, the results were controversial [44–46].

Naltrexone has been tested in amphetamine dependent subjects, and was found to attenuate significantly the subjective effects produced by dexamphetamine, and significantly block the craving for dexamphetamine [47]. Results from the same group in an open trial [48] showed a moderate effect and a RCT [49] showed that those taking naltrexone had a significantly higher number of negative urine samples and higher rate of continuous abstinence. Grant *et al.* [50] used N-acetyl cysteine plus naltrexone for methamphetamine dependence but did not detect any significant effects in a small group RCT ($n = 31$).

Naltrexone has been studied in nicotine dependence, also with controversial results [51–53]. In heavy marijuana smokers, naltrexone was found potentially to increase the abuse liability and cardiovascular risks of cannabinoids [54].

Naltrexone has been shown to reduce weight gain in mice [55], but subsequent RCTs in humans have not supported this effect [56, 57]. Recently, a combination regimen of naltrexone and bupropion has been tested, with a moderate effect in decreasing body weight [58, 59].

Naltrexone has been studied in pathologic gambling [60–62] with positive results, and positive results have also been seen with another opioid antagonist, nalmefene [63]. For internet addiction, one case report found that naltrexone had promising efficacy in suppressing a euphorically compulsive and interpersonally devastating addiction to internet pornography [64].

Since the major issue of concern for naltrexone’s efficacy on opioid and alcohol dependence is the medication compliance, its long-acting depot form was developed. In a review article [65], the authors concluded that naltrexone depot formulations have the potential to

improve significantly medication compliance in opioid and alcohol dependence, and in certain circumstances, they may constitute a promising new treatment option. In a recently published RCT [66], a naltrexone implant was trialled on patients with polydrug dependence, and the results showed that the active group had higher retention, decreased heroin and amphetamine use, and improved clinical condition.

The most common side effects reported with naltrexone are non-specific gastrointestinal complaints such as diarrhoea and abdominal cramping. Hepatotoxicity has been reported in high dose use [30]. Long term exposure (up to 3.5 years) to naltrexone may only selectively inhibit the pleasure associated with drinking alcohol and gambling, and not to listening to music, sex, reading, being with friends, eating good food, eating spicy food and playing video/card games [67].

Acamprosate

Acamprosate is a synthetic compound and an analogue of γ -aminobutyric acid (GABA) and taurine, and has been approved by the FDA in 2004 to treat alcohol dependence, years after its wide use in Europe. Pharmacologically, acamprosate binds to a specific spermidine-sensitive site that modulates the NMDA receptor in a complex way, and is regarded to be a 'partial co-agonist' [68]. This means that acamprosate is an indirect partial agonist of the NMDA-glutamate receptor, and antagonist of metabotropic glutamate receptors [69]. The concept is similar to the pharmacological effect of the dopamine D₂-receptor partial agonist aripiprazole on dopamine neurotransmission with a stabilizing effect, and is called a dopamine system stabilizer [70]. Acamprosate can be regarded as a glutamate system stabilizer and can decrease the craving for alcohol during withdrawal and abstinence [71]. A recently published systematic review based on 24 RCTs with 6915 participants [72] concluded that acamprosate appears to be an effective and safe treatment in alcohol dependent patients. Three trials compared acamprosate and naltrexone, and none of them indicated a superior effect of one drug over the other [72]. Acamprosate was not found to be effective for acute alcohol withdrawal symptoms in two RCTs [73, 74], indicating that it should be used after detoxification has been completed.

Acamprosate was trialled in a 9 week RCT design for cocaine dependence but the results were not encouraging [75]. In a small size ($n = 40$) RCT for binge eating disorder [76], acamprosate was not found to more beneficial than a placebo on any outcome variable. However the results of the endpoint and completer analyses suggested that the drug may have some utility in binge day frequency and measures of obsessive-compulsiveness of binge eating, food craving, and quality of life. In a small group trial, acamprosate did not prove effective in treating pathological gambling [77]. Currently no trials of acamprosate for other addictive disorders have been conducted. Interest-

ingly, acamprosate was shown to improve tinnitus in one RCT study [78], and it seemed to be effective in autistic disorder in an open trial of six subjects [79].

Topiramate

Topiramate is an anticonvulsant with a unique pharmacological profile including a blockage of voltage-dependent sodium channels, an augmentation of GABA activity at some subtypes of the GABA-A receptor, antagonism of the AMPA/kainate subtype of the glutamate receptor and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV. It has been hypothesized that these effects lead to neurostabilization and downstream reduction of dopamine release in the corticomesolimbic system and to possessing an anticraving effect. Shinn & Greenfield [80] published an extensive review on topiramate in the treatment of substance-related disorders, and summarized that topiramate is efficacious for the treatment of alcohol dependence, shows mixed results with nicotine dependence and promising effects on cocaine dependence. However, their findings are limited by the small sample size. A RCT for methamphetamine addiction found that topiramate did not appear to promote abstinence in methamphetamine users but it could reduce the amount taken and reduce relapse rates in those who were already abstinent [81]. There have been some RCTs [82–85] of topiramate for binge eating disorder or bulimia nervosa, and all of the results showed efficacy in decreasing the frequency of binge eating, and body weight was also decreased. The side effects of topiramate include paresthesia (numbness and tingling), nausea and psychomotor slowing, which has limited its widespread use as an anticraving medication.

Disulfiram

Disulfiram has been used for about 60 years in the treatment of alcoholism [86, 87]. Disulfiram inhibits aldehyde dehydrogenase (ALDH), which results in the accumulation of acetaldehyde on ethanol ingestion. This toxic metabolite produces aversive symptoms, such as flushing, nausea and vomiting and a desire to avoid this reaction encourages abstinence. This kind of reaction deters alcohol consumption and is categorized as 'aversive therapy' or a 'psychological threat' pill [88, 89]. Because 50–90% of patients who abuse cocaine also abuse alcohol [90], it was thought that discouraging alcohol consumption in cocaine- and alcohol-dependent individuals may also lower cocaine use. Indeed, disulfiram has been found to reduce alcohol and cocaine intake in this patient population [91, 92]. Surprisingly, further studies have revealed that disulfiram is also effective in treating cocaine addicts who do not consume alcohol [93].

It is likely that an ALDH-independent mechanism (non-aversive effect) is responsible for the ability of disulfiram to promote cocaine abstinence [94]. The mechanism of the anticraving effect of disulfiram is rather complex and many

hypotheses have been proposed. Schroeder *et al.* [95] used a laboratory animal model to investigate whether the inhibitory effect of disulfiram on dopamine β -hydroxylase (DBH), the catecholamine biosynthetic enzyme that converts dopamine to norepinephrine in noradrenergic neurons, underlies the drug's ability to treat cocaine dependence and whether it can prevent drug exposure and stress from precipitating relapse. Their results suggest that disulfiram's efficacy in the treatment of cocaine addiction is associated with the inhibition of DBH and interference with the ability of environmental stimuli to trigger relapse. Yao *et al.* [96] uncovered another potential effect of disulfiram through the inhibition of ALDH-2 by using a specific inhibitor, ALDH-2i. ALDH-2i blocks the conversion of 3,4-dihydroxyphenylacetaldehyde (DOPAL) to 3,4-dihydroxyphenyl-acetic acid (DOPAC) in the dopamine biosynthetic pathway, increasing DOPAL concentrations and tetrahydropapaveroline production, thereby inhibiting tyrosine hydroxylase to reduce dopamine biosynthesis. This in turn blunts the rewarding/reinforcing effects of cocaine and cocaine-associated cues.

An earlier study by Nagendra *et al.* [97] showed that the disulfiram metabolite DETC-MeSO could block glutamate binding to receptors in mouse brains. In addition, the disulfiram metabolite carbamathione is a partial non-competitive NMDA glutamate antagonist and does not inhibit ALDH-2. It has been found to possess an anticraving effect and has been proposed to be responsible for the efficacy of disulfiram in cocaine dependence [98].

Disulfiram has been trialled in pathological gambling in several case reports [99, 100] and the authors suggested that it deserves further investigation. No other addictive disorder has been trialled with disulfiram. Besides its anticraving effects, disulfiram is also an affordable and promising anticancer drug [101] and has potential therapeutic use for fungal infections [102].

Baclofen

Baclofen is a derivative of GABA and can activate the GABA_B receptor with no known abuse potential. It has muscle relaxant and sedative properties and is primarily used to treat spasticity of neurological disorders, such as spinal cord injury, cerebral palsy and multiple sclerosis [103]. Baclofen was first reported in one open ($n = 10$) [104] and one small scale ($n = 39$) RCT [105], and was proven to be effective in inducing abstinence from alcohol and reducing alcohol craving. Subsequently, the same group reported that baclofen was effective and well tolerated in alcohol-dependent patients with liver cirrhosis [106], and that a higher dose (20 mg three times daily) had a greater effect than the common dose (10 mg three times daily) [107]. However, in another larger scale RCT ($n = 80$) [108], baclofen was not found to be superior to placebo in percentage of heavy drinking days and days abstinent, time to first drink, or time to relapse to heavy drinking; while it was associated with a significant reduction in state anxiety in

the treatment of alcohol dependence. A very high dose (270 mg day⁻¹) of baclofen was suggested by Ameisen [109] in his own experience case report to suppress successfully the craving for alcohol. Recently, an article reported that a high dose (75–125 mg day⁻¹) regimen of baclofen was effective in four cases of treatment-resistant alcohol dependence [110]. To evaluate the effectiveness of a high dose of baclofen in the treatment of alcohol dependence, well controlled trials are warranted to confirm these findings [111, 112]. One multicentre trial of baclofen (60 mg day⁻¹) for abstinence initiation in severe cocaine dependence found negative results [113]. In a recent comprehensive review, the authors concluded that baclofen seems to be safe and well-tolerated, even in patients with liver cirrhosis [114]. In a 12 week RCT on opioid dependence [115], patients treated with baclofen had a higher retention rate and favourable responses of opioid craving, but no significant difference was seen in the rates of opioid-positive urine tests. Baclofen showed no effect on a laboratory model of marijuana withdrawal and relapse [116]. Baclofen has been trialled on contemplating smokers [117] and showed an effect of reducing cigarettes smoked per day in a 9 week RCT.

N-acetylcysteine

N-acetylcysteine (NAC) is used primarily as a mucolytic agent and in the management of paracetamol (acetaminophen) overdose. Through its metabolic contribution to glutathione production, cysteine participates in the general antioxidant activities of the body. NAC has also been shown to modulate neurotransmitter pathways, including glutamate and dopamine [118]. These properties are the hypothetical basis for NAC having an anticraving effect.

NAC has been trialled in a variety of psychiatric disorders such as schizophrenia, bipolar disorder and addictive disorders. The addictive disorders include cocaine [119–121], marijuana [122], nicotine [123], pathological gambling [124] and trichotillomania [125]. Most of these trials were small in scale; however, the results appear to be promising in the treatment of psychiatric disorders including addictive disorders. In the review article by Dean *et al.* [118], the authors suggested that NAC is a readily available and affordable nutritional supplement. Further research is warranted to clarify the appropriate dosing range and duration for specific disorders, and for any unforeseen side effects related to long term treatment.

Bupropion

Bupropion is a popular antidepressant in clinical practice. It is a derivative of substituted amphetamine and its primary pharmacological action is thought to be norepinephrine-dopamine re-uptake inhibition. Bupropion is also an antagonist of nicotine receptors [126] and is an efficacious medication for smoking cessation [127]. Patients on bupropion have reported less nicotine craving [128]. In the

treatment of methamphetamine dependence [129, 130], bupropion has only shown effectiveness in light users. Bupropion shows no effect on cocaine [131] or cannabis [132] dependence.

Bupropion has also shown a moderate effect in the treatment of obesity [133]. Seizure is a troublesome side effect and is highly dose-dependent. This side effect can be attenuated with the use of an extended release dosage form [134].

Others

Other medications which have been trialled include ondansetron (serotonin 5-HT₃-receptor antagonist) and tiagabine (GABAergic anticonvulsant). Ondansetron has shown a positive effect for early onset alcoholism [135], but not in the dependence of opioids [136], methamphetamine [137] and cocaine [138]. Tiagabine has been involved in trials for cocaine dependence with controversial results [139, 140].

Conclusion

Addiction is a chronic, relapsing disorder with heterogeneous conditions. Maintenance medications for addiction include substitution, aversive and anticraving drugs. However, some forms of addictive disorder are not only substance dependence, but by a broader definition include unhealthy behaviour such as pathological gambling, internet addiction, binge eating and trichotillomania. The pathophysiology of addiction is not well understood. It is generally believed that the reward system is involved in the formation of addiction, and that any compound that can modulate this system will have the potential to be an anticraving medication.

This review summarizes specific anticraving medications that have been involved in trials for different substance and behavioural addictive disorders. It is important to treat addictive patients with psychosocial intervention and anticraving medications can also play a role in relapse prevention. Further well-designed and larger scale RCTs are needed to examine the real efficacy of a specific compound to a specific addictive disorder.

Competing Interests

The author has no competing interests to declare regarding the content of this article.

The author Shih-Ku Lin has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declares he had support from the Taiwanese National Science Council for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previ-

ous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

This study was supported by NSC 95-2314-B-532-009-MY3. The author thanks Mr Yan-Lung Chui for his assistance in the preparation of the manuscript.

REFERENCES

- 1 American Society of Addiction Medicine. Definition of Addiction. Available at <http://www.asam.org/research-treatment/definition-of-addiction> (Short Definition of Addiction, last accessed on 27 June 2012).
- 2 Block JJ. Issues for DSM-V: internet addiction. *Am J Psychiatry* 2008; 165: 306–7.
- 3 Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, Jacobs WS, Kadish W, Manso G. Refined food addiction: a classic substance use disorder. *Med Hypotheses* 2009; 72: 518–26.
- 4 Potenza MN, Fiellin DA, Heninger GR, Rounsaville BJ, Mazure CM. Gambling: an addictive behavior with health and primary care implications. *J Gen Intern Med* 2002; 17: 721–32.
- 5 Mick TM, Hollander E. Impulsive-compulsive sexual behavior. *CNS Spectr* 2006; 11: 944–55.
- 6 Kozlowski LT, Mann RE, Wilkinson DA, Poulos CX. 'Cravings' are ambiguous: ask about urges or desires. *Addict Behav* 1989; 14: 443–5.
- 7 Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage* 2010; 49: 2536–43.
- 8 World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research. Geneva: WHO, 1993.
- 9 American Psychiatric Association Committee on Nomenclature and Statistics. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington, DC: American Psychiatric Association, 2000.
- 10 Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KP. Neural activity related to drug craving in cocaine addiction. *Arch Gen Psychiatry* 2001; 58: 334–41.
- 11 Fontenelle LF, Oostermeijer S, Harrison BJ, Pantelis C, Yucel M. Obsessive-compulsive disorder, impulse control disorders and drug addiction: common features and potential treatments. *Drugs* 2011; 71: 827–40.
- 12 Pelchat ML. Of human bondage: food craving, obsession, compulsion, and addiction. *Physiol Behav* 2002; 76: 347–52.
- 13 Rosenberg H. Clinical and laboratory assessment of the subjective experience of drug craving. *Clin Psychol Rev* 2009; 29: 519–34.
- 14 Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ. Stress-induced cocaine craving and

hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. *Arch Gen Psychiatry* 2006; 63: 324–31.

- 15 Huang MC, Chen CH, Liu HC, Chen CC, Ho CC, Leu SJ. Differential patterns of serum brain-derived neurotrophic factor levels in alcoholic patients with and without delirium tremens during acute withdrawal. *Alcohol Clin Exp Res* 2011; 35: 126–31.
- 16 Hilburn C, Nejtek VA, Underwood WA, Singh M, Patel G, Gangwani P, Forster MJ. Is serum brain-derived neurotrophic factor related to craving for or use of alcohol, cocaine, or methamphetamine? *Neuropsychiatr Dis Treat* 2011; 7: 357–64.
- 17 Heberlein A, Dursteler-MacFarland KM, Lenz B, Frieling H, Grosch M, Bonsch D, Kornhuber J, Wiesbeck GA, Bleich S, Hillemecher T. Serum levels of BDNF are associated with craving in opiate-dependent patients. *J Psychopharmacol* 2011; 25: 1480–4.
- 18 Sinha R. New findings on biological factors predicting addiction relapse vulnerability. *Curr Psychiatry Rep* 2011; 13: 398–405.
- 19 O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry* 2005; 162: 1423–31.
- 20 Schultz W. Dopamine signals for reward value and risk: basic and recent data. *Behavioral and brain functions*. *Behav Brain Funct* 2010; 6: 24.
- 21 Zweifel LS, Parker JG, Lobb CJ, Rainwater A, Wall VZ, Fadok JP, Darvas M, Kim MJ, Mizumori SJ, Paladini CA, Phillips PE, Palmiter RD. Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. *Proc Natl Acad Sci U S A* 2009; 106: 7281–8.
- 22 Blythe SN, Atherton JF, Bevan MD. Synaptic activation of dendritic AMPA and NMDA receptors generates transient high-frequency firing in substantia nigra dopamine neurons *in vitro*. *J Neurophysiol* 2007; 97: 2837–50.
- 23 Zhou TC, Geisler S, Marinelli M, Degarmo BA, Zahm DS. The mesopontine rostromedial tegmental nucleus: a structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. *J Comp Neurol* 2009; 513: 566–96.
- 24 Lavezzi HN, Zahm DS. The mesopontine rostromedial tegmental nucleus: an integrative modulator of the reward system. *Basal Ganglia* 2011; 1: 191–200.
- 25 Kauer JA, Malenka RC. Synaptic plasticity and addiction. *Nat Rev Neurosci* 2007; 8: 844–58.
- 26 Landsberg R, Taintor Z, Plumb M, Amico L, Wicks N. An analysis of naltrexone use – its efficacy, safety and potential. *NIDA Res Monogr* 1976; 9: 106–13.
- 27 Martin WR, Jasinski DR, Mansky PA. Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man. *Arch Gen Psychiatry* 1973; 28: 784–91.
- 28 Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, Bayliss S, Roberts T, Burls A. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11: 1–85.
- 29 Soyka M, Kranzler HR, van den Brink W, Krystal J, Moller HJ, Kasper S. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: opioid dependence. *World J Biol Psychiatry* 2011; 12: 160–87.
- 30 Gonzalez JP, Brogden RN. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs* 1988; 35: 192–213.
- 31 Sideroff SI, Charuvastra VC, Jarvik ME. Craving in heroin addicts maintained on the opiate antagonist naltrexone. *Am J Drug Alcohol Abuse* 1978; 5: 415–23.
- 32 Altshuler HL, Phillips PE, Feinhandler DA. Alteration of ethanol self-administration by naltrexone. *Life Sci* 1980; 26: 679–88.
- 33 Harris RA, Erickson CK. Alteration of ethanol effects by opiate antagonists. *Curr Alcohol* 1979; 5: 17–28.
- 34 O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry* 1992; 49: 881–7.
- 35 Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 1992; 49: 876–80.
- 36 Gonzales RA, Weiss F. Suppression of ethanol-reinforced behavior by naltrexone is associated with attenuation of the ethanol-induced increase in dialysate dopamine levels in the nucleus accumbens. *J Neurosci* 1998; 18: 10663–71.
- 37 Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 2001; 345: 1734–9.
- 38 O'Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, Rounsaville BJ, Wu R. Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. *Alcohol Clin Exp Res* 2007; 31: 625–34.
- 39 Gueorguieva R, Wu R, Pittman B, Cramer J, Rosenheck RA, O'Malley SS, Krystal JH. New insights into the efficacy of naltrexone based on trajectory-based reanalyses of two negative clinical trials. *Biol Psychiatry* 2007; 61: 1290–5.
- 40 Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, McCaul ME, Anthenelli R, Salloum I, Galloway G, Garbutt J, Swift R, Gastfriend D, Kallio A, Karhuvaara S. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 2004; 24: 421–8.
- 41 Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 1999; 56: 719–24.
- 42 Karhuvaara S, Simojoki K, Virta A, Rosberg M, Loyttyniemi E, Nurminen T, Kallio A, Makela R. Targeted nalmefene with

- simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 2007; 31: 1179–87.
- 43 Schmitz JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addict Behav* 2001; 26: 167–80.
 - 44 Schmitz JM, Stotts AL, Sayre SL, DeLaune KA, Grabowski J. Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *Am J Addict* 2004; 13: 333–41.
 - 45 Schmitz JM, Lindsay JA, Green CE, Herin DV, Stotts AL, Moeller FG. High-dose naltrexone therapy for cocaine-alcohol dependence. *Am J Addict* 2009; 18: 356–62.
 - 46 Hersh D, Van Kirk JR, Kranzler HR. Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology (Berl)* 1998; 139: 44–52.
 - 47 Jayaram-Lindstrom N, Konstenius M, Eksborg S, Beck O, Hammarberg A, Franck J. Naltrexone attenuates the subjective effects of amphetamine in patients with amphetamine dependence. *Neuropsychopharmacology* 2008; 33: 1856–63.
 - 48 Jayaram-Lindstrom N, Wennberg P, Beck O, Franck J. An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. *Nord J Psychiatry* 2005; 59: 167–71.
 - 49 Jayaram-Lindstrom N, Hammarberg A, Beck O, Franck J. Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *Am J Psychiatry* 2008; 165: 1442–8.
 - 50 Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. *Eur Neuropsychopharmacol* 2010; 20: 823–8.
 - 51 King A, de Wit H, Riley RC, Cao D, Niaura R, Hatsukami D. Efficacy of naltrexone in smoking cessation: a preliminary study and an examination of sex differences. *Nicotine Tob Res* 2006; 8: 671–82.
 - 52 David S, Lancaster T, Stead LF, Evins AE. Opioid antagonists for smoking cessation. *Cochrane Database Syst Rev* 2006; (4): CD003086.
 - 53 Covey LS, Glassman AH, Stetner F. Naltrexone effects on short-term and long-term smoking cessation. *J Addict Dis* 1999; 18: 31–40.
 - 54 Cooper ZD, Haney M. Opioid antagonism enhances marijuana's effects in heavy marijuana smokers. *Psychopharmacology (Berl)* 2010; 211: 141–8.
 - 55 Recant L, Voyles NR, Luciano M, Pert CB. Naltrexone reduces weight gain, alters 'beta-endorphin', and reduces insulin output from pancreatic islets of genetically obese mice. *Peptides* 1980; 1: 309–13.
 - 56 Atkinson RL, Berke LK, Drake CR, Bibbs ML, Williams FL, Kaiser DL. Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; 38: 419–22.
 - 57 Malcolm R, O'Neil PM, Sexauer JD, Riddle FE, Currey HS, Counts C. A controlled trial of naltrexone in obese humans. *Int J Obes* 1985; 9: 347–53.
 - 58 Wadden TA, Foreyt JP, Foster GD, Hill JO, Klein S, O'Neil PM, Perri MG, Pi-Sunyer FX, Rock CL, Erickson JS, Maier HN, Kim DD, Dunayevich E. Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity* 2011; 19: 110–20.
 - 59 Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376: 595–605.
 - 60 Kim SW, Grant JE, Adson DE, Shin YC. Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. *Biol Psychiatry* 2001; 49: 914–21.
 - 61 Grant JE, Kim SW, Hartman BK. A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 2008; 69: 783–9.
 - 62 Lahti T, Halme JT, Pankakoski M, Sinclair D, Alho H. Treatment of pathological gambling with naltrexone pharmacotherapy and brief intervention: a pilot study. *Psychopharmacol Bull* 2010; 43: 35–44.
 - 63 Grant JE, Odlaug BL, Potenza MN, Hollander E, Kim SW. Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *Br J Psychiatry* 2010; 197: 330–1.
 - 64 Bostwick JM, Bucci JA. Internet sex addiction treated with naltrexone. *Mayo Clin Proc* 2008; 83: 226–30.
 - 65 Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. *CNS Neurosci Ther* 2011; 17: 629–36.
 - 66 Tiihonen J, Krupitsky E, Verbitskaya E, Blokhina E, Mamontova O, Fohr J, Tuomola P, Kuoppasalmi K, Kiviniemi V, Zwartau E. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *Am J Psychiatry* 2012; 169: 531–36.
 - 67 O'Brien CP, Gastfriend DR, Forman RF, Schweizer E, Pettinati HM. Long-term opioid blockade and hedonic response: preliminary data from two open-label extension studies with extended-release naltrexone. *Am J Addict* 2011; 20: 06–12.
 - 68 Naassila M, Hammoumi S, Legrand E, Durbin P, Daoust M. Mechanism of action of acamprosate. Part I. Characterization of spermidine-sensitive acamprosate binding site in rat brain. *Alcohol Clin Exp Res* 1998; 22: 802–9.
 - 69 Mason BJ, Heyser CJ. The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. *Expert Opin Drug Saf* 2010; 9: 177–88.
 - 70 Hirose T, Kikuchi T. Aripiprazole, a novel antipsychotic agent: dopamine D2 receptor partial agonist. *J Med Invest* 2005; 52: (Suppl.): 284–90.

- 71** Littleton JM. Acamprosate in alcohol dependence: implications of a unique mechanism of action. *J Addict Med* 2007; 1: 115–25.
- 72** Rosner S, Hackl-Herrwerth A, Leucht S, Leherth P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 2010; (9): CD004332.
- 73** Gual A, Leherth P. Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol Alcohol* 2001; 36: 413–8.
- 74** Kampman KM, Pettinati HM, Lynch KG, Xie H, Dackis C, Oslin DW, Sparkman T, Sharkoski T, O'Brien CP. Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. *Addict Behav* 2009; 34: 581–6.
- 75** Kampman KM, Dackis C, Pettinati HM, Lynch KG, Sparkman T, O'Brien CP. A double-blind, placebo-controlled pilot trial of acamprosate for the treatment of cocaine dependence. *Addict Behav* 2011; 36: 217–21.
- 76** McElroy SL, Guerdjikova AI, Winstanley EL, O'Melia AM, Mori N, McCoy J, Keck PE, Jr, Hudson JI. Acamprosate in the treatment of binge eating disorder: a placebo-controlled trial. *Int J Eat Disord* 2011; 44: 81–90.
- 77** Dannon PN, Rosenberg O, Schoenfeld N, Kotler M. Acamprosate and baclofen were not effective in the treatment of pathological gambling: preliminary blind rater comparison study. *Front Psychiatry* 2011; 2: 33.
- 78** Azevedo AA, Figueiredo RR. Tinnitus treatment with acamprosate: double-blind study. *Braz J Otorhinolaryngol* 2005; 71: 618–23.
- 79** Erickson CA, Early M, Stigler KA, Wink LK, Mullett JE, McDougall CJ. An open-label naturalistic pilot study of acamprosate in youth with autistic disorder. *J Child Adolesc Psychopharmacol* 2011; 21: 565–9.
- 80** Shinn AK, Greenfield SF. Topiramate in the treatment of substance-related disorders: a critical review of the literature. *J Clin Psychiatry* 2010; 71: 634–48.
- 81** Elkashef A, Kahn R, Yu E, Iturriaga E, Li SH, Anderson A, Chiang N, Ait-Daoud N, Weiss D, McSherry F, Serpi T, Rawson R, Hrymiec M, Weiss D, McCann M, Pham T, Stock C, Dickinson R, Campbell J, Gorodetzky C, Haning W, Carlton B, Mawhinney J, Li MD, Johnson BA. Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction* 2012; 107: 1297–306.
- 82** Hoopes SP, Reimherr FW, Hedges DW, Rosenthal NR, Kamin M, Karim R, Capece JA, Karvois D. Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge and purge measures. *J Clin Psychiatry* 2003; 64: 1335–41.
- 83** McElroy SL, Hudson JI, Capece JA, Beyers K, Fisher AC, Rosenthal NR. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. *Biol Psychiatry* 2007; 61: 1039–48.
- 84** Claudino AM, de Oliveira IR, Appolinario JC, Cordas TA, Duchesne M, Sichieri R, Bacaltchuk J. Double-blind, randomized, placebo-controlled trial of topiramate plus cognitive-behavior therapy in binge-eating disorder. *J Clin Psychiatry* 2007; 68: 1324–32.
- 85** Nickel C, Tritt K, Muehlbacher M, Pedrosa Gil F, Mitterlehner FO, Kaplan P, Lahmann C, Leiberich PK, Krawczyk J, Kettler C, Rother WK, Loew TH, Nickel MK. Topiramate treatment in bulimia nervosa patients: a randomized, double-blind, placebo-controlled trial. *Int J Eat Disord* 2005; 38: 295–300.
- 86** Hald J, Jacobsen E. A drug sensitizing the organism to ethyl alcohol. *Lancet* 1948; 2: 1001–4.
- 87** Fuller RK, Branchey L, Brightwell DR, Derman RM, Emrick CD, Iber FL, James KE, Lacoursiere RB, Lee KK, Lowenstam I. Disulfiram treatment of alcoholism. A Veterans Administration Cooperative Study. *JAMA* 1986; 256: 1449–55.
- 88** Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; 26: 290–302.
- 89** Johnson BA. Medication treatment of different types of alcoholism. *Am J Psychiatry* 2010; 167: 630–9.
- 90** Closser MH, Kosten TR. Alcohol and cocaine abuse. A comparison of epidemiology and clinical characteristics. *Recent Dev Alcohol* 1992; 10: 115–28.
- 91** Carroll KM, Nich C, Ball SA, McCance E, Frankforter TL, Rounsaville BJ. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction* 2000; 95: 1335–49.
- 92** Carroll KM, Nich C, Ball SA, McCance E, Rounsaville BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 1998; 93: 713–27.
- 93** Carroll KM, Fenton LR, Ball SA, Nich C, Frankforter TL, Shi J, Rounsaville BJ. Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. *Arch Gen Psychiatry* 2004; 61: 264–72.
- 94** Gaval-Cruz M, Weinshenker D. Mechanisms of disulfiram-induced cocaine abstinence: antabuse and cocaine relapse. *Mol Interv* 2009; 9: 175–87.
- 95** Schroeder JP, Cooper DA, Schank JR, Lyle MA, Gaval-Cruz M, Ogbonmwan YE, Pozdeyev N, Freeman KG, Iuvone PM, Edwards GL, Holmes PV, Weinshenker D. Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine beta-hydroxylase. *Neuropsychopharmacology* 2010; 35: 2440–9.
- 96** Yao L, Fan P, Arolfo M, Jiang Z, Olive MF, Zablocki J, Sun HL, Chu N, Lee J, Kim HY, Leung K, Shryock J, Blackburn B, Diamond I. Inhibition of aldehyde dehydrogenase-2 suppresses cocaine seeking by generating THP, a cocaine use-dependent inhibitor of dopamine synthesis. *Nat Med* 2010; 16: 1024–8.
- 97** Nagendra SN, Faiman MD, Davis K, Wu JY, Newby X, Schloss JV. Carbamoylation of brain glutamate receptors by a disulfiram metabolite. *J Biol Chem* 1997; 272: 24247–51.
- 98** Kaul S, Faiman MD, Lunte CE. Determination of GABA, glutamate and carbamithione in brain microdialysis samples by capillary electrophoresis with fluorescence detection. *Electrophoresis* 2011; 32: 284–91.
- 99** Mutschler J, Buhler M, Grosshans M, Diehl A, Mann K, Kiefer F. Disulfiram, an option for the treatment of pathological gambling? *Alcohol Alcohol* 2010; 45: 214–6.

- 100** Muller CA, Banas R, Heinz A, Hein J. Treatment of pathological gambling with disulfiram: a report of 2 cases. *Pharmacopsychiatry* 2011; 44: 81–3.
- 101** Lin LZ, Lin J. Antabuse (disulfiram) as an affordable and promising anticancer drug. *Int J Cancer* 2011; 129: 1285–6.
- 102** Sauna ZE, Shukla S, Ambudkar SV. Disulfiram, an old drug with new potential therapeutic uses for human cancers and fungal infections. *Mol Biosyst* 2005; 1: 127–34.
- 103** Davidoff RA. Antispasticity drugs: mechanisms of action. *Ann Neurol* 1985; 17: 107–16.
- 104** Addolorato G, Caputo F, Capristo E, Colombo G, Gessa GL, Gasbarrini G. Ability of baclofen in reducing alcohol craving and intake: II – preliminary clinical evidence. *Alcohol Clin Exp Res* 2000; 24: 67–71.
- 105** Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol* 2002; 37: 504–8.
- 106** Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; 370: 1915–22.
- 107** Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedogni G, Caputo F, Gasbarrini G, Landolfi R. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol Alcohol* 2011; 46: 312–7.
- 108** Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2010; 34: 1849–57.
- 109** Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol* 2005; 40: 147–50.
- 110** Pastor A, Jones DM, Currie J. High-dose baclofen for treatment-resistant alcohol dependence. *J Clin Psychopharmacol* 2012; 32: 266–8.
- 111** Enserink M. Addiction research. Anonymous alcoholic bankrolls trial of controversial therapy. *Science* 2011; 332: 653.
- 112** Rolland B, Bordet R, Cottencin O. Alcohol-dependence: the current French craze for baclofen. *Addiction* 2012; 107: 848–9.
- 113** Kahn R, Biswas K, Childress AR, Shoptaw S, Fudala PJ, Gorgon L, Montoya I, Collins J, McSherry F, Li SH, Chiang N, Alathari H, Watson D, Liberto J, Beresford T, Stock C, Wallace C, Gruber V, Elkashef A. Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend* 2009; 103: 59–64.
- 114** Gorsane MA, Kebir O, Hache G, Blecha L, Aubin HJ, Reynaud M, Benyamina A. Is baclofen a revolutionary medication in alcohol addiction management? Review and recent updates. *Subst Abus* 2012; 33: 336–49.
- 115** Assadi SM, Radgoodarzi R, Ahmadi-Abhari SA. Baclofen for maintenance treatment of opioid dependence: a randomized double-blind placebo-controlled clinical trial. *BMC Psychiatry* 2003; 3: 16.
- 116** Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Cooper ZD, Foltin RW. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)* 2010; 211: 233–44.
- 117** Franklin TR, Harper D, Kampman K, Kildea-McCrea S, Jens W, Lynch KG, O'Brien CP, Childress AR. The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. *Drug Alcohol Depend* 2009; 103: 30–6.
- 118** Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci* 2011; 36: 78–86.
- 119** LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, Saladin M, McRae A, Brady K. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. *Am J Addict* 2006; 15: 105–10.
- 120** LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A, Brady K, Kalivas PW, Malcolm R. Is cocaine desire reduced by N-acetylcysteine? *Am J Psychiatry* 2007; 164: 1115–7.
- 121** Mardikian PN, LaRowe SD, Hedden S, Kalivas PW, Malcolm RJ. An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry* 2007; 31: 389–94.
- 122** Gray KM, Watson NL, Carpenter MJ, LaRowe SD. N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. *Am J Addict* 2010; 19: 187–9.
- 123** Schmaal L, Berk L, Hulstijn KP, Cousijn J, Wiers RW, van den Brink W. Efficacy of N-acetylcysteine in the treatment of nicotine dependence: a double-blind placebo-controlled pilot study. *Eur Addict Res* 2011; 17: 211–6.
- 124** Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. *Biol Psychiatry* 2007; 62: 652–7.
- 125** Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2009; 66: 756–63.
- 126** Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. *J Pharmacol Exp Ther* 2000; 295: 321–7.
- 127** Tonnesen P, Tonstad S, Hjalmarson A, Leborg F, Van Spiegel PI, Hider A, Sweet R, Townsend J. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med* 2003; 254: 184–92.
- 128** Kotlyar M, Drone D, Thuras P, Hatsukami DK, Brauer L, Adson DE, al'Absi M. Effect of stress and bupropion on

- craving, withdrawal symptoms, and mood in smokers. *Nicotine Tob Res* 2011; 13: 492–7.
- 129 Elkashef AM, Rawson RA, Anderson AL, Li SH, Holmes T, Smith EV, Chiang N, Kahn R, Vocci F, Ling W, Pearce VJ, McCann M, Campbell J, Gorodetzky C, Haning W, Carlton B, Mawhinney J, Weis D. Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology* 2008; 33: 1162–70.
 - 130 Shoptaw S, Heinzerling KG, Rotheram-Fuller E, Steward T, Wang J, Swanson AN, De La Garza R, Newton T, Ling W. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 2008; 96: 222–32.
 - 131 Margolin A, Kosten TR, Avants SK, Wilkins J, Ling W, Beckson M, Arndt IO, Cornish J, Ascher JA, Li SH, Bridge P. A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 1995; 40: 125–31.
 - 132 Carpenter KM, McDowell D, Brooks DJ, Cheng WY, Levin FR. A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict* 2009; 18: 53–64.
 - 133 Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, Hilton L, Suttrop M, Solomon V, Shekelle PG, Morton SC. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; 142: 532–46.
 - 134 Fava M, Rush AJ, Thase ME, Clayton A, Stahl SM, Pradko JF, Johnston JA. 15 years of clinical experience with bupropion HCl: from bupropion to bupropion SR to bupropion XL. *Prim Care Companion J Clin Psychiatry* 2005; 7: 106–13.
 - 135 Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Bordnick PS, Ait-Daoud N, Hensler J. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *JAMA* 2000; 284: 963–71.
 - 136 Sell LA, Cowen PJ, Robson PJ. Ondansetron and opiate craving. A novel pharmacological approach to addiction. *Br J Psychiatry* 1995; 166: 511–4.
 - 137 Johnson BA, Ait-Daoud N, Elkashef AM, Smith EV, Kahn R, Vocci F, Li SH, Bloch DA, Methamphetamine Study Group. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *Int J Neuropsychopharmacol* 2008; 11: 1–14.
 - 138 Johnson BA, Roache JD, Ait-Daoud N, Javors MA, Harrison JM, Elkashef A, Mojsiak J, Li SH, Bloch DA. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug Alcohol Depend* 2006; 84: 256–63.
 - 139 Gonzalez G, Desai R, Sofuoglu M, Poling J, Oliveto A, Gonsai K, Kosten TR. Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine dependent methadone-treated patients. *Drug Alcohol Depend* 2007; 87: 1–9.
 - 140 Winhusen T, Somoza E, Ciraulo DA, Harrer JM, Goldsmith RJ, Grabowski J, Coleman FS, Mindrum G, Kahn R, Osman S, Mezinskis J, Li SH, Lewis D, Horn P, Montgomery MA, Elkashef A. A double-blind, placebo-controlled trial of tiagabine for the treatment of cocaine dependence. *Drug Alcohol Depend* 2007; 91: 141–8.