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Review

New achievements and pharmacotherapeutic approaches in the treatment of alcohol dependence

Falk Kiefer *, Karl Mann

University of Heidelberg, Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health (CIMH), J5, D-68159 Mannheim, Germany

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Abstract

The treatment of alcohol dependence mainly consists of psychological, social, and pharmacotherapeutic interventions aiming to reduce physical withdrawal, craving, and alcohol relapse. During the last years, it has become increasingly clear that adjuvant pharmacotherapy is efficacious especially in rehabilitation programs for alcohol dependent patients. The development of alcohol dependence seems to involve adaptive changes in amino acid neurotransmitter systems, stimulation of dopamine and opioid peptide systems, and changes in serotonergic activity. Disulfiram, naltrexone and acamprosate are approved treatments for the management of abstinence maintenance treatment. New compounds are under investigation. This review discusses the neurobiological basis of alcohol addiction, pharmacological targets for relapse prevention treatment and pre-clinical and clinical results with the most promising drugs.

Keywords: Alcohol; Relapse prevention; Addiction; Treatment; Pharmacotherapy

Contents

* Corresponding author. Tel.: +49 621 1703 3522; fax: +49 621 1703 3505.
E-mail address: kiefer@zi-mannheim.de (F. Kiefer).

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1. Introduction

Alcohol addiction is a chronic disorder that develops on a genetic, psychosocial and environmental background. Whereas alcohol withdrawal treatment is widely accepted as a pharmacotherapeutic domain, anti-craving and relapse prevention treatment in clinical practice up to now is mainly based on psychosocial and psychotherapeutic interventions consisting of individual and group therapy, self-help groups and cognitive–behavioural interventions.

However, there is growing interest in the interaction of psychotherapy with drug therapy since it has been shown repeatedly that pharmacological treatment is efficacious in the reduction of craving and risk of relapse in abstinent alcohol dependent patients (Mann, 2004; Kiefer et al., 2004; Spanagel and Mann, 2005).

Drugs have been developed on the basis of knowledge of the biological mechanisms of alcohol dependence. Currently approved drugs are disulfiram, acamprosate, and naltrexone in the US and in the majority of European Countries. Drugs acting on dopaminergic (tiapride, lisuride and flupenthixol) and serotonergic mechanisms (buspirone, fluoxetine nefazodone, ritanserin and ondansetron) have been studied in clinical trials but are not currently approved for the treatment of alcohol dependence. Mood stabilizers and anticonvulsants (e.g. carbamazepine and topiramate), as well as sedative–anxiolytics (e.g. benzodiazepines and γ-hydroxybutyric acid), have also been proposed to be of benefit, but again these agents are not approved for use in this indication. Future research possibilities include drugs acting at other subtypes of opiate receptors, calcium channel blockers, cholinergic drugs such as galanthamine, cannabinoid receptor antagonists, and neuropeptidergic drugs. None of these agents have yet been evaluated satisfactorily in the clinic.

This review discusses the neurobiological basis of alcohol addiction, pharmacological targets for relapse prevention treatment and pre-clinical and clinical results with the most promising compounds.

2. Neurobiology of alcohol addiction

For many years alcohol was suggested to exert its neurobiological effects mainly by increasing membrane fluidity, altering the function of macro-molecules in the cell membrane. However, new evidence indicates that alcohol binds to hydrophobic pockets of proteins, modulating their function by changing their 3-dimensional structure. Proteins that are particularly sensitive to this effect include ion-channels, neurotransmitter receptors, and enzymes involved in signal transduction (Gordis, 1998). Neurotransmitters and receptors with notable sensitivity to this effect include dopamine, serotonin, γ-aminobutyric-acid (GABA), glutamic acid and opioids, adenosine, neuropeptide Y, nor-epinephrine, cannabinoid receptors, and opioid peptides (Koob et al., 1998). These neurotransmitter systems involved in the different components of alcohol dependence are potential targets for the development of therapeutic drugs for the treatment of alcoholism (Spanagel and Zieglgänsberger, 1997).

Important neurochemical targets for the acute effects of alcohol are the facilitation of inhibitory GABAergic, and inhibition of excitatory glutamatergic neurotransmission. Potentiation of GABAergic inhibition is widely accepted to underlie the acute sedative effects of alcohol. Long-term adaptive changes in these two neurotransmitter transmitter systems to the sedative effects of alcohol are thought to underlie the development of alcohol dependence. In response to chronic exposure to alcohol, there is a compensatory up-regulation of the glutamatergic system and a down-regulation of the GABAergic system resulting in an increased tolerance for alcohol (Grobin et al., 1998).

However, when alcohol is abruptly withdrawn, a state of hyper-excitability emerges, perceived by the subject as a disagreeable state of arousal, anxiety and sleeplessness. This is the core of the negative affective state which the alcoholic patient will drink to relieve. These plastic changes in the brain, brought about by changes in protein synthesis, are only slowly reversible. This may explain the persistence of negative craving during alcohol withdrawal, and why stable abstinence after acute detoxification is so difficult to achieve.

The dopaminergic system was also shown to play a central role in the biology of alcoholism. Dopaminergic mesolimbic dopamine A10 neurones are activated by alcohol consumption, resulting in a release of the neurotransmitter in the limbic system and mediating positive reinforcement and reward (Gessa et al., 1985). It is postulated that during the development of alcohol dependence, dopamine neurones can be sensitised to cues that elicit drinking. Changes in the reactivity of dopamine neurones to alcohol may mediate the increase in the desirability and reward of drinking, and thus stabilise consummatory behaviour.

The opioid system seems to play a modulatory role on the dopaminergic system, whereby activation of opiate receptors stimulates the release of dopamine in the brain. Drinking alcohol increases the release of endorphins, endogenous opioid peptides, in the brain thus indirectly activating the dopaminergic reinforcement/reward system (Benjamin et al., 1993). It has been postulated that individual differences in the sensitivity of endogenous opioid systems may underlie individual differences in intensity of craving for alcohol, and in the risk of becoming alcohol dependent (Gianoulakis, 1996).

The cholinergic system is also implicated in the acute effects of alcohol, as well as in the long-term changes seen in chronic alcoholism. Ethanol interacts with the nicotinic acetylcholine receptor to facilitate receptor activation (Cardoso et al., 1999). Activation of nicotinic receptors on dopaminergic neurones (Söderpalm et al., 2000) may explain the interaction between smoking and alcohol addiction. In chronic alcoholism, excitotoxic damage to cholinergic neurones in the basal forebrain attenuates cholinergic function (Arendt, 1994).

A role for serotonin in the neurochemical effects of alcohol has also been proposed some years ago (Sellers et al., 1992). The activity of the serotonergic (5-HT) system is positively related with impulsivity (Soubrié, 1986). Support for the relevance of this concept for human behaviour is supported by the efficacy of selective serotonin reuptake inhibitors (SSRI) in

the treatment of obsessive–compulsive disorders. The similarities between obsessive–compulsive disorders and alcohol addiction have been noted by several authors (Anton et al., 1995).

3. Currently approved drugs

3.1. Disulfiram

The first drug therapy for alcoholism to be proposed was disulfiram that was serendipitously discovered to be an agent causing alcohol aversion in Ohio rubber workers in 1939. This drug (and the related calcium carbimide) prevents the metabolism of alcohol, causing an accumulation of acetaldehyde resulting in hypotension, flushing, nausea, and vomiting when patients consume alcohol. The objective of disulfiram treatment is thus to create an aversion to alcohol, rather than to modulate its neurochemical effects. Many studies have been performed with disulfiram, but few are controlled or of high quality. Controlled clinical trials have yielded inconsistent results, and have failed to demonstrate unambiguously a therapeutic benefit of treatment in enhancing abstinence (Garbutt et al., 1999). However, since it is the psychological deterrent effect of the drug rather than its biological effect that is useful, it is difficult to envisage how its efficacy could be demonstrated in a classical double-blind, placebo-controlled trial. In an attempt to address this issue, the Veterans Administration cooperative study compared randomised 605 patients to either placebo no drug, 1 mg disulfiram (an inactive dose) or 250 mg disulfiram (the standard dose) (Fuller et al., 1996). There was no difference in either the proportion of patients remaining abstinent or in the time to first relapse between the three groups. However, the patients receiving disulfiram 250 mg had fewer drinking days once they had relapsed than did the other two groups. Moreover, embedded in an outpatient treatment program with high-frequency short-term individual therapeutic contacts, initially daily, co-administration of aldehyde dehydrogenase inhibitors seems to have positive treatment effects (Ehrenreich et al., 1997).

Given the physiological impact of acetaldehyde intoxication and potential associated risk, alcohol-dependent patients treated with disulfiram have to be monitored carefully.

3.2. Naltrexone

Naltrexone is an opiate receptor antagonist that is thought to reduce the positively reinforcing, pleasurable effects of alcohol and to reduce craving. Thirteen years ago, two small clinical placebo-controlled trials demonstrated a reduced rate of relapse to heavy drinking, reduced craving and less frequent drinking in naltrexone-treated patients (O'Malley et al., 1992; Volpicelli et al., 1992). During the following years, several other trials have been performed. An increase in time to first relapse has been the most consistent finding obtained with naltrexone, although not all trials, including two of the largest (Gastpar et al., 2002; Krystal et al., 2001), have been positive. Many of the studies have also measured the proportion of patients who remain abstinent (i.e. no alcohol consumption at all), or the time to first alcohol consumption. Even though these were not the primary efficacy criteria of the studies, these data are useful as they permit comparisons with the acamprosate database, where absolute abstinence, rather than relapse into heavy drinking, has been the efficacy criterion. Within each study, data on these measures are generally coherent with treatment effects on the time to first relapse. Studies in patients with concomitant substance dependence have failed to show any benefit from naltrexone (Hersh et al., 1998).

Several factors may explain the discrepancies in results of the different clinical trial results with naltrexone. Naltrexone was found to be more effective in patients receiving training in coping skills than in those receiving supportive therapy alone O'Malley et al. 1992; Balldin et al., 2003; Heinälä et al., 2001. However, an Australian study demonstrated that efficacy could be observed without intensive structured psychosocial support (Latt et al., 2002). Some studies have indicated that naltrexone treatment was most effective in patients with suffering from craving; moreover, craving was diminished by treatment with naltrexone (O'Malley et al., 1992; Anton et al., 1999; Chick et al., 2000a,b; McCaul et al., 2000; Monti et al., 1999). Of course, compliance was also shown as an important predictor of outcome (Anton et al., 1999; Chick et al., 2000a,b; Volpicelli et al., 1997; Monti et al., 2001). For example, in the study by Monti et al. (2001), a significant treatment effect was only demonstrated when non-compliant subjects were excluded from the analysis. A large multi-site double-blind, placebo-controlled trial with an injectable sustained release formulation demonstrated that relapse to heavy drinking decreased in patients receiving this depot preparation compared to placebo (Garbutt et al., 2005). Such preparations may have a place in the treatment of poorly compliant patients. Three studies have demonstrated that the effect of naltrexone on relapse to heavy drinking has a tendency to fade in the months following the end of treatment (Monti et al., 2001; O'Malley et al., 1996; Anton et al., 2001). However, the Finnish study has shown the effect can be maintained if naltrexone is taken punctually at moments of strong craving (Heinälä et al., 2001).

A conceptual framework for integrating the clinical data on naltrexone has been proposed by Sinclair (2001), who suggested that naltrexone is useful for handling relapses rather than at maintaining absolute abstinence, and thus that contingency of drinking alcohol and taking naltrexone is important in bringing to light treatment effects. A systematic meta-analysis of 24 placebo-controlled trials presented in 32 papers with a total of 2861 patients treated concluded that naltrexone produced a consistent decrease in relapse rate to heavy drinking and in drinking frequency, although it did not appear to enhance abstinence (Srisurapanont and Jarusuraisin, 2005).

3.3. Acamprosate

Acamprosate, calcium acetyl homotaurinate, is available in the US and most European countries for the maintenance of abstinence in recently detoxified alcoholics. The mechanism

of action involves primarily the restoration of a normal *N*-methyl-D-aspartate (NMDA) receptor tone in glutamatergic systems (Rammes et al., 2001). It decreases postsynaptic potentials in the neocortex (Zeise et al., 1993), and diminishes voluntary alcohol intake in alcohol preferring rats (Gewiss et al., 1991).

Littleton (1995) proposed that one of acamprosate's actions is suppressing conditioned withdrawal craving by its effects on calcium channels and on NMDA receptors. Acamprosate was investigated in sixteen controlled published trials with about 4000 patients up to now (Mann et al., 2004). A further study has been performed in the United States of America (Johnson and Ait-Daoud, 2000); however, results have not yet been published. Studies have produced consistent results showing acamprosate treatment to be superior to placebo in maintaining abstinence. In all but three published controlled clinical studies, the proportion of treated patients abstaining at the end of the study was twice as high as for patients receiving placebo. Treatment periods of up to a year have been studied. In addition, studies of Sass et al. (1996) and of Whitworth et al. (1996) have evaluated long-term abstinence one year after the end of the treatment period and shown the treatment effects to be maintained. Two of the negative studies, Rousseaux et al. (1996) and Namkoong et al. (2003), were small and possibly underpowered. The absence of effect in the other negative study (Chick et al., 2000a,b), which was the largest of all published trials with acamprosate, may be attributable to the latency in initiating treatment. The study drug was introduced after a long stabilisation period (25 days) which followed acute weaning. However, during this period, a substantial proportion of patients had already resumed drinking. This was the only study that used such a design. However, there was some evidence for a reduction of craving in patients treated with acamprosate in this study, as well as in the studies of Pelc et al. (1997) and Paille et al. (1995).

A literature-based meta-analysis, in which the original clinical trial data from seventeen trials were re-analysed (Mann et al., 2004), concluded that acamprosate was effective, and suggested that that the treatment effect could increase with time.

3.4. Differential treatment effects of naltrexone and acamprosate

The effects of naltrexone and acamprosate appear to relate to different aspects of drinking behaviour, with the former stabilising abstinence and the latter decreasing alcohol consumption. There is little direct comparative data on the relative benefits of the two treatments. A recent head-to-head study performed in Spain (Rubio et al., 2001) suggested that naltrexone was more efficacious in preventing relapse to heavy drinking. However, the conclusions from this trial should be interpreted cautiously, since the study was not blinded and there was imbalance in the drop-out rate. A placebo-controlled, double-blind study found both naltrexone and acamprosate to increase the time to first drink and time to first relapse into heavy drinking compared to placebo, without showing a significant differential treatment effect (Kiefer et al., 2003). A large comparative study addressing this issue involving over one thousand patients (the COMBINE study) is currently underway in the United States of America.

4. Drugs currently not approved

Several other potential therapies have been evaluated in alcohol dependence, of which none has yet provided unambiguous proof of efficacy. Most relevant are listed in this chapter.

4.1. Nalmefene

Nalmefene is an opiate receptor antagonist with similar pharmacological properties to naltrexone but lower occurrence of side-effects, especially regarding hepatotoxicity. A small pilot study in 21 patients showed this drug to have some beneficial effect on relapse to heavy drinking (Mason et al., 1994). This finding was reproduced in a larger study in 105 patients receiving cognitive behavioural therapy and either 20 or 80 mg of nalmefene (Mason et al., 1999). A more recent study in Finland, comparing 40 and 10 mg nalmefene with placebo, showed a reduction in frequency of heavy drinking with the high dose but not the low dose of this opiate receptor antagonist (Mäkelä et al., 2001). As with naltrexone, the treatment effect seemed to wane as time went by.

4.2. Dopaminergic drugs

Dopaminergic drugs are effective in animal models of alcohol dependence, but evidence of clinical effectiveness in man is scanty. Dopamine receptor antagonists (neuroleptics) are of use during the acute detoxification phase to prevent agitation and attenuate hallucinations and *delirium tremens*. One such drug that been widely used in this context is tiapride (Peters and Faulds, 1994). This drug was originally studied in two small placebo-controlled clinical trials as an adjunct to psychotherapy for long-term rehabilitation. In one of these studies, the treatment period was one month (Shaw et al., 1994), and, in the other, six months (Shaw et al., 1987). Both showed increased abstinence and reduced alcohol consumption. However, a much larger double-blind placebo-controlled trial performed in Germany, which involved 299 patients, showed no difference (Gastpar et al., unpublished). Also a study evaluating the effect of a depot injection of flupenthixol decanoate has recently been performed (Wiesbeck et al., 2001). This included 281 patients and demonstrated a significant reduction in the proportion of patients remaining totally abstinent after six months of treatment (14.8% on active treatment compared with 34.5% on placebo). Moreover, a large trial applying placebo controlled treatment with lisuride, a dopamine D2 receptor agonist, in patients suffering from alcoholism revealed shortened abstinence duration compared with placebo treatment (Schmidt et al., 2002). These results compromise the future of dopamine receptor antagonists outside the context of symptom management during acute withdrawal.

4.3. Serotonergic drugs

A number of drugs acting on serotonergic neurotransmission have been studied in alcohol dependence, since serotonin is widely implicated in a variety of consummatory behaviours and impulsivity. These agents are either selective serotonin reuptake inhibitors (fluoxetine, sertraline or citalopram) or drugs acting at serotonin receptors (buspirone, ritanserin, ondansetron and nefazodone). Most of these studies suffer from small patient numbers, and relatively short treatment periods. Selective serotonin reuptake inhibitors, despite being effective in animals and in reducing alcohol appetence in non-alcoholic humans, have proved disappointing. Five studies have investigated fluoxetine, all but one in patients without comorbid depression. The first of these used a fixed-interval drinking paradigm in 20 alcoholic inpatients locked in a hospital ward for one month (Gorelick and Paredes, 1992). Although at the study end, there was no difference in alcohol consumption between treatment groups, a reduction in craving was reported in the fluoxetine-treated group. The three subsequent studies used a more naturalistic treatment setting: two of these reported no benefit of fluoxetine treatment (Kranzler et al., 1995; Kabel and Petty, 1996), while the third described a higher proportion of patients abstinent at the end of a two month treatment period in the fluoxetine group (Janiri et al., 1996). In the one study which evaluated patients suffering from ongoing major depressive episodes, however, fluoxetine significantly ameliorated drinking behaviour, probably as a consequence of treating the underlying depression (Cornelius et al., 1997). Two studies have evaluated citalopram in non-depressed patients (Naranjo et al., 1995; Tiihonen et al., 1996). One study reported superior treatment retention, and self-reported drinking with citalopram (Tiihonen et al., 1996); whereas, the other (Naranjo et al., 1995), which used more stringent outcome measures of drinking behaviour, found no difference between treatment groups. The most recent studies concern sertraline. The first study (Roy, 1998) followed 36 well-supervised inpatients with comorbid alcoholism and major depression for two months, only one of whom drank during the study period. No conclusion could thus be drawn about the efficacy of sertraline. The second (Pettinati et al., 2001) followed a cohort of 100 outpatients stratified for presence or absence of a lifetime depressive episode. There was some evidence for a beneficial effect of sertraline on alcohol consumption in the patients without a history of depression, but not in those with previous depressive episodes. The most recent study (Coşkunol et al., 2002) studied patients without psychiatric comorbidity treated as outpatients for six months. Although the drinking outcome measures were somewhat soft, significantly more abstinent days were reported in the sertraline-treated group.

Concerning the receptor agonists and antagonists, no evidence of clinical efficacy in alcohol-dependence has been obtained with ritanserin (Johnson et al., 1996; Wiesbeck et al., 1999) or nefazodone (Kranzler et al., 2000). The two negative ritanserin studies had a large sample size, used validated outcome measures and were of sufficient duration to demonstrate any potential treatment effect. The 5-HT_{1A} receptor antagonist buspirone has been evaluated in five trials. Three of these (Tollefson et al., 1992; Kranzler et al., 1994; Malcolm et al., 1992) included patients with comorbid generalised anxiety disorder, alcohol dependence being the only DSM (Diagnostic and Statistical Manual of Mental Disorders) inclusion criterion in the other two (Bruno, 1989; Malec et al., 1996a,b). Identification of potential effects on alcohol consumption was the primary goal of four of the studies, whereas in the fifth (Tollefson et al., 1992) evolution of anxious symptoms was the primary goal, and effects on drinking were only assessed according to the physician's impression. None of the studies demonstrated a significant effect on the primary alcohol-related outcome measure, although three revealed improved retention in treatment programs (Tollefson et al., 1992; Kranzler et al., 1994; Bruno, 1989). A significant reduction in alcohol consumption was also observed in one study of anxious patients (Kranzler et al., 1994). A meta-analysis of studies performed with buspirone concluded that any efficacy of this drug was secondary to an anxiolytic effect, rather than on drinking behaviour per se (Malec et al., 1996a,b). Finally, ondansetron, a 5-HT_3 receptor antagonist, seems to be the exception, with two trials having demonstrated some efficacy on measures of drinking frequency and intake in early-onset alcoholics (Sellers et al., 1995; Johnson et al., 2000). These trials were however quite short (6 weeks and 12 weeks), and long-term efficacy needs to be confirmed.

4.4. Mood stabilizers and anticonvulsants

Mood stabilizers and anticonvulsants depress alcohol consumption in experimental animals. However, clinical trials have not provided clear evidence of efficacy for the majority of compounds. Lithium carbonate was studied in one of the largest trials ever conducted in alcohol dependence (457 patients), but no effect on drinking behaviour was observed (Dorus et al., 1989). The safety profile of lithium is, in any case, probably incompatible for use in outpatient treatment of alcohol dependence. More promising are results with non-benzodiazepine anticonvulsants such as carbamazepine, valproic acid, gabapentin, vigabatrin and topiramate (Book and Myrick, 2005). Carbamazepine has shown efficacy in a small study on alcohol consumption (Mueller et al., 1997); however, this finding deserves confirmation in a larger trial. Topiramate was suggested to antagonise rewarding effects of alcohol by inhibiting mesocorticolimbic dopamine release via facilitation of γ-amino-butyric acid activity and inhibition of glutamate function. In a clinical study with 150 participants, topiramate recipients reported increased abstinence and less craving than placebo recipients (Johnson et al., 2004). However, the tolerability of the drug was limited mainly due to somnolence, dizziness, ataxia, related speech problems, and psychomotor slowing; it remains uncertain whether approval studies are intended by the licence holder.

4.5. Sedative/anxiolytics

Benzodiazepines and other GABA-ergic drugs are useful in managing acute withdrawal, but are not useful in rehabilitation.

Their sedative properties may indeed be harmful in alcoholics, as they could substitute for alcohol itself. A study of γ-hydroxybutyric acid performed in Italy (Gallimberti et al., 1992) has shown that three month treatment during rehabilitation can increase the proportion of abstinent patients. A larger multi-centre study of γ-hydroxybutyric acid is ongoing. However, it should be noted that this drug is used as a recreational street drug in the United States of America.

5. Combination therapies

Little information is available on the utility of combinations of different pharmacological agents in the treatment of alcohol dependence. A prerequisite of such studies is that the therapeutic impact of each treatment alone be well established. This is not the case for most potential drug treatments. Combined treatment with acamprosate and disulfiram has been studied by Besson et al. (1998). Although allocation of patients to disulfiram was not randomised, results suggest that concomitant administration of disulfiram improves the effectiveness of acamprosate on relapse prevention. Combined treatment of naltrexone and disulfiram has been evaluated in the treatment in patients with alcohol dependence and comorbid psychiatric disorder (Petrakis et al., 2005). Whereas both drugs showed an efficacy in the reduction of alcohol intake, no advantage appeared when both drugs had been combined. Potential benefits of combination therapy with naltrexone and acamprosate have been shown in a recently completed study in 160 patients (Kiefer et al., 2003). This demonstrated that the proportion of patients remaining completely abstinent at the end of the twelve-week treatment-period was around twice as high in the group receiving both medications than in the groups receiving naltrexone or acamprosate alone. Both treatments alone were, however, superior to placebo (Kiefer and Wiedemann, 2004). A recent small study (20 patients) of combination therapy with naltrexone and odansetron in alcohol-dependent patients suggested a positive effect of combined treatment on the reduction of craving (Ait-Daoud et al., 2001).

6. Safety

Both drugs approved for the treatment of alcohol dependence, naltrexone and acamprosate, are generally well-tolerated. Drop-out rates for adverse events in clinical trials have generally been low, with the exception of one study with naltrexone, which reported a drop-out rate of 41%, significantly higher than the 21% observed in placebo-treated patients (Kranzler et al., 2000). The principle side-effect of acamprosate is diarrhoea. The principal side-effects of naltrexone are nausea, fatigue and headache (Croop et al., 1997). Nausea is reported by around 10% of patients. The occurrences of these side-effects are important determinants of compliance (Monti et al., 1999). Naltrexone can be hepatotoxic and caution should be exercised in giving this drug to patients with liver-disease, and their liver function should be monitored periodically throughout treatment. Nonetheless, in practice, hepatic impairment is not observed more frequently in alcohol-dependent patients taking naltrexone (Croop et al., 1997).

Disulfiram, on the other hand, is not well-tolerated. This drug inhibits alcohol dehydrogenase, and the resulting build-up of acetaldehyde in the organism produces an array of side-effects, some of which may give cause for concern in certain patient populations. These side-effects include tremor, unstable blood pressure, diarrhoea, nausea and possibly severe vomiting. Disulfiram should not be prescribed in patients with hypertension, diabetes, heart disease, a history of stroke, peripheral neuropathy, epilepsy or renal or hepatic insufficiency.

7. Conclusions

Based on the data presented one can conclude that there is clear evidence of the concept and, moreover, of the efficacy of pharmacotherapy in the rehabilitation of alcohol dependent patients. The evidence for a beneficial effect is strongest for two compounds, naltrexone and acamprosate. Both drugs should be prescribed as an additive treatment to psychosocial support. However, interaction of pharmacotherapy with psychotherapy has to be elucidated further, since there is evidence that specific psychotherapeutic intervention may reinforce the effects of medication. Since we have up to now no valid data on differential treatment effect, drug therapy should be considered for all patients with alcohol dependence who do not have medical contraindications to the use of drugs and who are willing to take it. In patients with underlying psychiatric conditions, especially depression and anxiety, specific treatments for these should be used. At least, the optimal duration of relapse prevention treatment remains to be determined.

Although at the moment there is no clear evidence for an improved effect of polypharmacy, the future of management of alcoholism may be combination therapy, using drugs acting on different neuronal pathways involved in the development or maintenance of alcohol dependence. Given the large proportion of alcohol dependent subjects responding insufficiently to monotherapy with either acamprosate or naltrexone with the consequence of early relapse after detoxification, patients might benefit from enhancing the efficacy of relapse prevention treatment by combining acamprosate and naltrexone. However, further studies on combination therapy are warranted.

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