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Recommended Drug Treatment Strategies for the Alcoholic Patient

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Abstract

Significant progress has been made in the pharmacotherapy of alcoholism, specifically in the areas of withdrawal reaction, decreasing consumption, relapse prevention, and comorbid psychiatric illnesses. Psychosocial interventions are an important component of treatment strategies, and studies into the efficacy of medications often include psychotherapy or other nonpharmacological modalities. Increasingly, however, the evidence reveals the effectiveness of drug treatments for various components of the illness.

Many different pharmacological agents and dosage regimens have been investigated for the treatment of the alcohol withdrawal syndrome. The effectiveness and simplicity of giving long-acting benzodiazepines, using a loading-dose technique, make this regimen first-line therapy.

Both naltrexone (an opioid antagonist) and acamprosate (calcium acetylhomotaurinate) increase rates of abstinence and decrease relapse rates in alcohol-dependent individuals who are in abstinence-orientated programmes. If patients enter a comprehensive treatment programme, either naltrexone or acamprosate should be considered as an option in the treatment plan. The choice of medication is most likely to be determined by the availability of each, which differs considerably throughout the world. Selective serotonin (5-hydroxytryptamine; 5-HT)

reuptake inhibitors (SSRIs) seem to have short term effects, and are more effective in depressed alcoholics-dependent and in men. For all medications there is wide variability in treatment response (i.e. effect size) and compliance seems to be essential for successful treatment.

Preliminary evidence suggests the usefulness of pharmacotherapy in treating alcohol dependence in the presence of other comorbid psychiatric illnesses. Antidepressants have shown efficacy in the treatment of alcoholism with comorbid depression, as has buspirone for the treatment of comorbid chronic anxiety symptoms. Further understanding of the neurobiological mechanisms of dependence in animals and humans as well as improved knowledge of predictors of treatment response will lead to improvements in the pharmacotherapy of alcohol dependence.

This article reviews the pharmacological strategies that have been directed towards the treatment of alcohol dependence, focusing on the areas of intoxication, withdrawal syndrome, decreasing consumption, relapse prevention and comorbid psychiatric illnesses. Progress in the pharmacotherapy of alcohol dependence and related problems has been made through the integration of basic and clinical pharmacological strategies. Studies in animals and humans indicate relationships between serotonin (5-hydroxytryptamine; 5-HT), dopamine, glutamate, γ-aminobutyric acid (GABA) and endogenous opioids with the start, continuance and stopping of alcohol consumption.[1] Although most researchers have focused on one neurotransmitter system, a behaviour as complex as alcohol dependence probably involves several neurotransmitters.

1. Diagnosis

Alcoholic patients are more frequent users of medical services than the general population.[2] This readily available access to individuals with alcohol-related problems puts physicians in an excellent position to diagnose the illness.[3] Evaluation for alcoholism should be viewed as an integral part of a medical or psychiatric assessment in all patients. The ideal strategy should include a clinical interview which involves screening questions for alcohol problems, as well as inquiring into the quantity and frequency of alcohol consumption. Standard screening tests for alcoholism include the Michigan Alcoholism Screening Test (MAST)[4] and the CAGE questionnaire.[5] The CAGE is a brief, 4-item test that consists of 4 yes/no questions:

- Have you ever felt you should **cut** down on your drinking?
- Have people **annoyed** you by criticising your drinking?
- Have you ever felt bad or **guilty** about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**eye-opener**)?

A score of 1 or more on the CAGE questionnaire, or a history of large quantity or high frequency of alcohol consumption, should lead the clinician to a further, more detailed evaluation of alcoholism. This includes additional history to fully characterise the extent of drinking, and identify the presence of alcohol withdrawal symptoms, anxiety, depression or other comorbid psychiatric or medical illnesses.

In addition, a physical examination and laboratory tests are indicated to support the results of the assessment.[3] Useful signs to identify on physical examination include: abnormal skin vascularisations, hand tremor, rhinophyma, hepatomegaly and signs of past or present injury.[6,7] Serum γ-glutamyltransferase (GGT)[8,9] and mean corpuscular volume (MCV)[9,10] have been identified as objective markers of alcoholism; however, they have low sensitivity for the identification of less severe alcoholism.[11-13]

2. Alcohol Intoxication

Alcohol intoxication is a major cause of traffic accidents, suicides and hospital admissions.[14] The search for an alcohol antagonist has been in progress since the time when the ancient Greeks believed that the precious stone amethyst could block or reverse its behavioural effects; hence the term 'amethystic' agent. However, today there are many ethical and legal problems with allowing intoxicated individuals to drive cars, operate machinery or drink alcohol excessively without the perception of harm.

A single amethystic agent may never be found because alcohol affects various classes of synaptic receptors, neurotransmitters and neurohormones. Specific agents that have been investigated as alcohol antagonists in humans include: levodopa, aminophylline (theophylline ethylenediamine), ephedrine, naloxone, lithium, calcium antagonists, fructose[15,16] and more recently pyridoxine.[17] Initial results could not be replicated or confirmed for any of these agents.[1] Therefore, acute alcohol intoxication is usually treated with supportive care.[1]

3. Alcohol Withdrawal Syndrome

When alcohol intake is abruptly discontinued or reduced and blood alcohol concentrations decrease rapidly, a characteristic withdrawal syndrome results. The severity of the reaction varies with the intensity and duration of the preceding alcohol exposure. The symptoms of a mild reaction are tremor, insomnia and irritability lasting 48 hours or less, which, in a severe reaction, are followed by hallucinations, seizures and delirium tremens.[1,18] While controlled studies have confirmed the potency of nonpharmacological interventions such as monitoring of signs and symptoms and general nursing care,[19] patients with a history of withdrawal seizures or comorbid illness,[20] or those in moderate to severe withdrawal, should also receive pharmacotherapy,[18,21] as summarised in table I.[1,18,20,22-37]

A nationwide survey in the US of 176 inpatient alcohol treatment programmes revealed a wide variety of treatment regimens being used.[38] The most commonly used medications were the benzodiazepines, including chlordiazepoxide (33%), diazepam (16%) and the shorter-acting oxazepam (7%) and lorazepam (4%). Others included barbiturates (11%), phenytoin (10%), clonidine (7%), β-adrenoceptor antagonists (3%), carbamazepine (1%) and antipsychotics (1%). 52% of the programmes used a fixed dosage regimen with additional doses as needed, and only 9% used a front-loading dose technique.

Earlier studies described the effectiveness of the diazepam loading dose technique in which patients with moderate to severe withdrawal are administered 20mg of oral diazepam hourly until they show clinical improvement or become mildly se-

Table I. Alcohol intoxication and withdrawal

	Medication	Comments	References
Intoxication	None	Supportive care only	1
Alcohol withdrawal syndrome	Long-acting benzodiazepine (e.g. diazepam or chlordiazepoxide)	Loading dose technique is effective, simple and tolerated, and lowers the duration of treatment and total dose, e.g. diazepam 20mg PO hourly until improved or mildly sedated. Drug of choice, other than in the elderly or in severe liver disease	1,20,22,23
	Lorazepam	Drugs of choice in the elderly or in severe liver disease	24
	Clonidine	Superior to placebo, but inconsistent compared with benzodiazepines	25-29
	Atenolol	Superior to placebo, but additional evidence not available	30
	Carbamazepine	Probably efficacious, but adverse effects limit routine use	18,31-34
	Chlormethiazole	Less effective and less well tolerated than benzodiazepines	18,35
	Barbiturates	Good evidence of efficacy; however, narrow safety margin limits use	36,37

PO = orally.

dated.[1,22] This approach was supported by a double-blind, controlled trial of 101 inpatients who were randomised to either fixed-schedule therapy of chlordiazepoxide 4 times daily or to symptom-triggered therapy in which medication was given hourly in the presence of continued symptoms (which in essence resembles the loading dose technique, except that asymptomatic patients received no further medication). The mean duration of treatment, as well as the total dose of chlordiazepoxide, was significantly lower in the symptom-triggered group (9 *vs* 68 hours, and 100 *vs* 425mg, respectively).[23]

In clinical situations where impaired hepatic metabolism is a concern (e.g. the elderly, liver disease), it appears that lorazepam is the best tolerated benzodiazepine given that it does not undergo hepatic oxidation, and thus has more predictable pharmacokinetics.[24] Recently released practice guidelines recommend benzodiazepines for the treatment of alcohol withdrawal syndrome, with β-blockers, clonidine, carbamazepine and antipsychotics used only as adjunctive therapy. Symptom-triggered therapy was the preferred regimen, with structured assessment scales for monitoring.[20]

Several medications have undergone randomised trials for evaluation in the treatment of alcohol withdrawal syndrome. Clonidine (an α_2-adrenoceptor agonist) has been reported to be superior to placebo;[25] however, when it was compared with benzodiazepines in double-blind studies, the results were inconsistent with regard to efficacy and preventing complications.[26-29] Atenolol has also been found to be superior to placebo for the treatment of alcohol withdrawal,[30] but no further investigations have been done.

Double-blind studies comparing carbamazepine and oxazepam in the treatment of alcohol withdrawal syndrome found similar efficacy;[31,32] however, concerns about the methodology in these studies,[33] as well as adverse effects,[34] have limited the utility of carbamazepine as a routine treatment.[18] There is evidence that barbiturates are efficacious in this application,[36] but a narrow margin of safety raises concerns about their routine use.[37] Chlormethiazole is a sedative-hypnotic agent that has been used for the treatment of alcohol withdrawal syndrome in Europe.[18] Studies have shown it to be superior to placebo, but these results are inconsistent, and concerns that it is less effective and less well tolerated than benzodiazepines[35] have limited its widespread use.

Research continues into other treatments for alcohol withdrawal syndrome, based on various theories about the cause of the syndrome. Specific modalities that have been investigated include: analgesic nitrous oxide,[39-41] phenytoin,[42,43] valproic acid (sodium valproate),[34,44] flumazenil[45,46] calcium antagonists,[47-49] 5-HT_3 antagonists,[50] *N*-methyl-D-aspartate (NMDA) receptor antagonists,[18,51] dexamethasone,[52] tiapride[53] and testosterone.[54] Data on the benefit of these pharmacotherapies are limited at this time and further studies are required. However, none appears to provide significant benefit over benzodiazepines.

4. Decreased Consumption and Relapse Prevention

Numerous types of medications to decrease alcohol consumption and prevent clinical relapse have been tested, many of which are summarised in table II.[55-95] The choice of which medication to use is not only based on the evidence, but is also dependent on the availability of medications, which often differs markedly in different regions of the world.

4.1 Naltrexone

A large body of research has described the role of the endogenous opioid system in alcohol consumption. Some studies have shown that the reinforcing properties of drinking alcohol are related, in part, to increases in endogenous opioid activity following alcohol use,[96] thus hypothesising a mechanism for opioid antagonist therapy.[97] Genetically determined differences in endogenous opioid response to alcohol intake have also been related to risk of alcoholism.[98]

In late 1994, naltrexone became the first drug in over 40 years to be approved in the US for treating

Table II. Medications used to decrease alcohol consumption and prevent clinical relapse

Medication	Comments	References
Naltrexone	Approved for treating alcohol dependence	55
	Reduces consumption in heavy social drinkers	56-58
	Increases abstinence, lowers relapse rates and may have an anticraving effect	59-66
	Contraindicated in severe liver disease, or in the presence of acute infection or immunodeficiency	67
	Increase monitoring if used by women of childbearing age, or in patients with polysubstance abuse	67
	Start at 25 mg/day with increase in 2 days to 50 mg/day	67
Acamprosate	Approved in Europe	68
	Increases abstinence, may have anticraving effect	69-73
	Contraindicated in pregnant or lactating women, renal or severe hepatic impairment, children and the elderly	74
	Dosage of 1.3 g/day if <60kg bodyweight and 2 g/day if >60kg, with 1y duration	71,72,74
Fluoxetine	No benefit, with possible worse outcomes	75-78
Citalopram	Transient effects with no improvements in outcome. More effective in men than in women	79-82
Fluvoxamine	Poorly tolerated, thus limiting use	83
Ondansetron	May reduce the desire to drink	84,85
	At a dosage of 0.25mg bid, reduces consumption in mildly to moderately alcohol-dependent individuals	86
Ritanserin	In social drinkers, improves some alcohol-related measures but limited effect on alcohol intake	87
Alcohol-sensitising agents [disulfiram, calcium carbimide (calcium cyanamide)]	Clinical use being challenged given no apparent benefit over placebo, poor compliance	88-91
	May be effective when compliance is assured by regular supervision in a structured programme	91-93
Bromocriptine	Long-acting injectable shows no benefit in relapse prevention	94
	Oral route appears to reduce craving in those with specific D2 receptor genotype	95

bid = twice daily.

alcohol dependence.[55] A combined analysis of the original 2 trials[59,60] that led to approval was recently reported. In a total of 186 patients, naltrexone showed significant differences over placebo with regard to abstinence at the end of the 12-week treatment period (54 *vs* 31%) and time to first episode of heavy drinking.[61] A 6-month post-treatment follow-up of 80 patients in the study by O'Malley et al.[62] showed the naltrexone group to have higher abstinence levels at 1 month (67 *vs* 40%), lower relapse rates at 4 months (35 *vs* 57%) and fewer patients meeting criteria for alcohol abuse (10 *vs* 24%) or dependence (13 *vs* 39%) at 6 months.[62] Reanalysis of the original trials showed that, while treatment with naltrexone did not significantly reduce the likelihood of sampling alcohol, it did significantly reduce the rates of clinical relapse[63] and that this was probably due to lower levels of craving,[64] as well as reports of feeling less 'high' after drinking.[65]

In a more recent double-blind trial, 97 alcohol-dependent individuals were given psychosocial treatment and randomly assigned to naltrexone or placebo for 12 weeks in an outpatient setting. This more naturalistic design, where compliance was not ensured, showed naltrexone overall to have nonsignificant effects in reducing relapse rates (53 *vs* 35%) and number of drinking days (6 *vs* 11%), with significant improvement in drinking outcomes only in those who were highly compliant with the medication.[66]

Interindividual variability in response to naltrexone has been observed; thus, another area of investigation with naltrexone is patient/treatment

matching. Studies have suggested that naltrexone showed more benefit in patients with high baseline craving,[63,99] somatic distress[63] and poorer cognitive functioning.[99] An ongoing study is attempting to identify a relationship between a noninvasive measurement of endogenous opioid activity and response to naltrexone. The effect of naloxone when combined with alcohol expectancy on an individual's response to pain is being evaluated as a possible biological predictor of response in a double-blind, placebo-controlled trial of naltrexone plus cognitive behavioural therapy.[100]

Population studies in the US found 15 to 21% of men and 5 to 6% of women to be frequent drinkers.[56] Some investigators have therefore focused on the effects of naltrexone on alcohol consumption, hypothesising that it may be useful in the secondary prevention of alcohol dependence. Studies in social or nondependent heavy drinkers have revealed a number of changes with patients taking naltrexone while using alcohol, which include: reduced craving,[56,57] an aversive effect[57,58] and greater subjective intoxication,[58] as well as lower total consumption and fewer heavy drinking days.[56] These data, however, are insufficient to make recommendations regarding the use of naltrexone in nondependent heavy drinkers.

Issues relevant to the clinical use of naltrexone have been well summarised in a recent risk-benefit assessment.[67] Naltrexone is a pure opioid antagonist with no agonist activity and therefore no abuse potential. No evidence of tolerance or dependence has been found. There is little concern about drug-drug interactions since the major metabolite (6-β-naltrexol) is not metabolised via the cytochrome P450 enzyme system. It has an excellent safety profile, with the most common adverse effects being nausea and vomiting and less commonly headache, anxiety and fatigue. These often resolve within days and may represent a mild opioid withdrawal reaction. Suggestions have therefore been made that the regimen should start at a dosage of 25 mg/day, with an increase to the full 50 mg/day after 2 days.

Initial concerns regarding hepatotoxicity were based on reported increases in transaminases in studies of patients taking naltrexone 300 mg/day; however, the majority were asymptomatic, and all resolved when the drug was stopped.[101,102] There is no evidence of hepatotoxicity at recommended dosages[60] but, given the concerns, naltrexone is contraindicated in the presence of acute hepatitis, or during marked liver damage or failure. Other concerns include use by women of childbearing age who should have their birth-control methods monitored, since naltrexone stimulates luteinising hormone (LH) which may lead to unexpected ovulation. In addition, due to naltrexone increasing cortisol levels, patients with acute infection or immunodeficiency must weigh the risks and benefits of the treatment in this situation, as these are not known. If there is concern about initiating an opioid withdrawal syndrome in the presence of polysubstance use, a naloxone challenge test should be performed before starting therapy. Patients should be instructed to wear a notice identifying them as using naltrexone, explaining that it is an opioid antagonist and that therefore much greater doses of opiates would be needed if these are required in an emergency.

Drawing on the effectiveness of naltrexone that has already been described, there are several further issues that require exploration. A study in animals has shown the usefulness of periodic naltrexone[103] and some have suggested resuming treatment in patients during high-risk periods after the recommended initial 12-week treatment period.[104] Another consideration is combination pharmacotherapy, with a recent trial comparing naltrexone with sertraline versus naltrexone alone in 18 alcoholic patients.[105] However, the group receiving combination treatment showed no further improvement in several drinking outcomes and relapse over those receiving naltrexone alone. Optimal length of therapy, effectiveness with only minimal psychosocial intervention, initiation during inpatient programmes and higher doses all require further study.[104]

4.2 Nalmefene

Studies using other opioid antagonists, specifically nalmefene (nalmetrene), have shown promis-

ing results. In a 12-week, double-blind, randomised, placebo-controlled trial of 21 alcohol-dependent patients, those receiving nalmefene 40 mg/day had significantly lower rates of relapse, and a greater number of abstinent days.[106] Nalmefene was well tolerated and has potential advantages over naltrexone, including no dose-dependent hepatotoxicity and more effective binding to central opiate receptors.

4.3 Acamprosate

Acamprosate (calcium acetyl-homotaurinate) is another medication which has attracted much attention over the past few years, especially in Europe where it has been approved for the treatment of alcoholism.[68] Although not yet fully understood, it appears to act by several mechanisms, including inhibiting hyperexcitation of excitatory amino acids (e.g. glutamate),[69] reducing calcium ion fluxes, increasing GABA uptake, increasing serotonin levels, and noradrenergic antagonism.[74]

Four randomised, double-blind, placebo-controlled trials with a total of 1453 detoxified alcohol-dependent patients, lasting 3 to 27 months, have recently been published.[69-72] The treatment groups consistently showed significantly higher rates of continuous abstinence (33 *vs* 15%), mean duration of abstinence [the percentage of days a patient is abstinent divided by the total number of days in the study (48 *vs* 34%)] and retention in study [the number of patients who remain in the study for its duration (51 *vs* 38%)] compared with the controls. Even though the results are significant, the size of the effect (acamprosate-placebo) was relatively small (18, 14 and 13%, respectively). Several of these studies suggested an anticraving effect, with one finding significantly lower psychological dependence in the treatment group.[72] Similar results of significantly increased abstinence rates and retention in study were found from a pooled analysis of 11 trials involving 3338 patients.[73]

Specific issues pertaining to the clinical use of acamprosate have been summarised in a recent review.[74] Usually, the recommended dosage is 1.3 g/day for patients who are <60kg, and 2 g/day for those >60kg, to be taken in 3 divided doses with meals.[74] However, in the absence of adequate dose-response relationship studies, dosage recommendations are empirical. Two studies failed to show any significant differences in results between dosages of 1.3 and 2 g/day,[71,72] and although there were trends towards a better outcome at the higher dosage,[72] compliance may be a problem since diarrhoea, the most common adverse effect, is dose-dependent.[71] Treatment should be started soon after detoxification, with a recommended duration of 1 year. Acamprosate has an excellent safety profile, as there is no evidence of addictive potential or overdose toxicity, and a low risk of drug-drug interactions since it is not metabolised, but directly excreted in the urine. Acamprosate is contraindicated in pregnant or lactating women, and in patients with renal impairment or severe hepatic failure. Due to limited experience in the elderly, its use should be avoided.

4.4 Serotonergic Drugs

Studies in animals and humans indicate the importance of serotonergic neurotransmission in the regulation of alcohol consumption.[107] Several selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, fluvoxamine and citalopram, have been investigated in terms of decreasing alcohol consumption and preventing relapse.

Fluoxetine 60 mg/day has been tested in 2 recent randomised, double-blind, placebo-controlled trials involving a total of 129 alcohol-dependent patients.[75,76] Both trials showed that treatment did not reduce rates of relapse; in fact, one study revealed a trend towards lower abstinence rates in the fluoxetine group,[75] with the other showing greater compliance and retention in study for the placebo group.[76] A reanalysis of one study displayed poorer drinking-related outcomes in the treatment group among those characterised as being type B alcoholics (i.e. early onset and greater alcohol-related problems).[77] Another trial involving fluoxetine 60 mg/day for 2 weeks showed no effect on decreasing consumption in nonmoti-

vated, mildly to moderately dependent alcoholic individuals.[78]

A double-blind study in mild to moderate alcohol-dependent patients given citalopram 40 mg/ day or placebo for 12 weeks with a brief psychosocial intervention showed a significant reduction in alcohol intake only during the first week of citalopram. Thereafter, both placebo and citalopram groups reduced their drinking similarly, thus putting the clinical utility of citalopram into question.[79] Further analysis of this study revealed a significantly greater response to citalopram in men than in women after 12 weeks of treatment.[80] Two studies in severely alcohol-dependent patients revealed some improvement in drinking behaviours in those receiving citalopram 40 mg/day, though these did not translate into significantly lower abstinence rates.[81,82] Other studies using citalopram without a brief psychosocial intervention have shown that individual responses vary to a large degree, with no specific patient characteristics predicting response.[108,109]

In 2 trials using fluvoxamine, 18 of the 26 patients receiving active drug dropped out, mostly due to adverse effects.[83] Thus, the effect of SSRIs is usually short term.

It has been hypothesised that serotonin antagonists reduce the reinforcing effects of alcohol and decrease the desire to drink.[1] Pretreatment with ondansetron (a 5-HT_3 receptor antagonist) in healthy volunteers and social drinkers was found to augment certain stimulant, sedative and pleasurable effects following a standard dose of alcohol.[84,85] Patients reported a decreased desire to drink, possibly mediated by increased intoxication and/or aversive effects. In a 6-week, double-blind, placebo-controlled trial in which all patients were taught coping skills, ondansetron 0.25mg twice daily was found to significantly reduce the number of drinks per drinking day in those with a baseline drinking level of <10 drinks per day. No effect was found in the group receiving ondansetron at a dosage of 4 mg/day.[86]

Pretreatment with ritanserin (a 5-HT_2 receptor antagonist) in healthy volunteers, followed by a dose of alcohol, showed no change in CNS-depressant effects.[110] 39 heavy social drinkers were randomised, in a double-blind fashion, to either ritanserin 5 or 10 mg/day or placebo, with no other treatment. There was slightly less desire for alcohol in the 5 mg/day group, and decreased liking of alcohol in the 10 mg/day group. However, neither treatment showed significant effects on outpatient alcohol intake.[87] These results suggest that ritanserin has limited efficacy for reducing heavy drinking.

4.5 Alcohol Sensitisers

Currently, 2 pharmacotherapies widely used in clinical practice to maintain abstinence are the alcohol-sensitising agents disulfiram and calcium carbimide (cyanamide). These drugs inhibit hepatic aldehyde dehydrogenase (ALDH), causing increased blood acetaldehyde levels after alcohol ingestion. The result is a highly unpleasant episode of flushing, weakness and nausea.[1] At present their efficacy is being questioned given that several large trials failed to show any benefit over placebo, and that nonpharmacological factors appeared to explain the earlier findings.[88-90]

A review of 24 studies with oral disulfiram, and 14 with implanted disulfiram, concluded that the evidence for the use of this drug was equivocal, with most studies using poor methodology.[91] In addition, poor compliance with these medications has put in doubt their clinical effectiveness. If compliance is assured by regular supervision, then disulfiram has shown a benefit in decreasing alcohol consumption and increasing total abstinent days.[92] Some, therefore, suggest a role for the use of disulfiram in the context of a structured programme with contracts and meaningful incentives for compliance.[91,93] Factors limiting the use of disulfiram and calcium carbimide include several contraindications (e.g. severe liver disease, pregnancy, heart disease, greater age), CNS and liver toxicity, and multiple drug-drug interactions[111-113]

4.6 Other Agents

There is evidence of altered dopamine function in alcoholic patients both when drinking and when

detoxified.[114] Long-acting injectable bromocriptine (a dopamine D_2 receptor antagonist) was recently studied in a double-blind, placebo-controlled trial with 366 moderately and severely alcohol-dependent patients being randomised to 6 monthly injections of bromocriptine 25 or 50mg, or placebo. No significant differences in rates of relapse were found between the treatment groups.[94] In another trial, oral bromocriptine was given to alcoholic individuals in a double-blind, placebo-controlled design. Interestingly, a reduction in craving occurred in the actively treated patients who were found to have the A_1 allele of the D_2 receptor.[95] This again raises the issue of potential patient treatment matching, in this instance involving a specific genotype.

Other medications recently investigated in relapse prevention include 4-hydroxybutyric acid (GHB),[115] interferon[116] and nitrous oxide.[117] Although preliminary results are encouraging, they all used open-label designs or were plagued by poor methodology. Of additional concern is that both GHB and nitrous oxide have an abuse potential, which is likely to limit their role in this patient population.

5. Treatment of Alcohol Dependence with a Comorbid Psychiatric Diagnosis

Alcohol dependence is often associated with a comorbid psychiatric diagnosis. In a survey of 928 alcohol-dependent men seen at a Veterans Administration Centre, 62% met lifetime diagnostic criteria for at least one other psychiatric illness.[118] Several of these illnesses and possible treatments are presented in table III.[119-130]

5.1 Depression

A recent large survey of alcohol-dependent individuals found a history of primary depression in 15.2% of the group and secondary depression in 26.4%.[131] Primary depression is defined by the first episode of depression having occurred before the onset of alcohol abuse or occurring during periods of prolonged abstinence.[120]

Imipramine was assessed in a 12-week open trial involving 60 alcoholic patients with primary depression, and 45% showed improvement in both mood and drinking.[119] The responders from this trial were then eligible for a randomised, placebo-controlled, double-blind discontinuation study which revealed a trend towards decreased relapse in the treatment group. In a second randomised, placebo-controlled trial involving similar patients, no overall effect on drinking was found; however, reduced consumption was evident in those with improved mood.[120] Unfortunately, a 25% dropout rate in the treatment group due to oversedation and anticholinergic adverse effects remains an obstacle for imipramine use.

Desipramine was studied in a 6-month, placebo-controlled, double-blind trial involving 71 detoxified patients with alcohol dependence, 28 of whom

Table III. Comorbid psychiatric diagnoses associated with alcohol dependence

Diagnosis	Medication	Comments	References
Depression	Imipramine	May reduce alcohol use in patients whose primary depression improves	119
		Adverse effects result in high dropout rate	120
	Desipramine	Good efficacy in treating secondary depression, with possible lower relapse rates	121
	Fluoxetine	Reduces alcohol consumption, with lower relapse rates and improvements in depression	122,123
Anxiety disorder	Buspirone	Improvements in both drinking outcomes and anxiety symptoms	124,125
Post-traumatic stress disorder	Sertraline	Preliminary results show reductions in psychiatric symptoms and improvements in drinking outcomes	126
Antisocial personality disorder	Nortriptyline	Limited evidence finds higher abstinence rates and lower consumption only in those with a concurrent mood or anxiety disorder	127,128
Bipolar affective disorder	Valproic acid (sodium valproate)	Small study suggests improvement in mood and reduced consumption	129,130

had secondary depression.[121] Results showed a significant improvement in mood symptoms among the depressed patients, as well as a trend towards a decrease in relapse to alcohol drinking in both treatment groups.

An open trial involving 12 depressed alcohol-dependent individuals, treated with fluoxetine at 20 to 40 mg/day for 8 weeks, resulted in significant improvements in depression and alcohol consumption.[122] A 12-week, double-blind study randomised 51 depressed alcoholics to fluoxetine 20 mg/day or placebo, and found that treatment with fluoxetine had significant effects in lowering alcohol consumption, increasing time to first episode of heavy drinking, and decreasing depressive symptoms.[123]

These results, in combination with those from the tricyclic antidepressant trials, provide strong support for the pharmacological treatment of depression occurring in the alcoholic patient. Some researchers have suggested that, since a majority of depressions resolve once detoxification is complete, clinicians wait for 2 weeks of abstinence before starting any antidepressants.[132,133] In contrast, others have shown the stability of depression in alcoholic individuals over time,[134] and that the presence of either primary or secondary depression at entry into treatment for alcoholism increased the rate of relapse, and decreased time to first drink.[135] Further trials are thus required to provide more clarity in this area.

5.2 Anxiety Disorders

In the Epidemiological Catchment Area survey[136] 19.4% of those with a history of alcohol abuse or dependence also had a lifetime diagnosis of an anxiety disorder. Evidence suggests that anxiety is likely to be both a cause and a consequence of alcoholism.[137] Nonpharmacological treatments are indicated for managing transient anxiety symptoms, with medications recommended for the treatment of chronic anxiety disorders.

Buspirone, a 5-HT_{1A} partial agonist, has been used in the treatment of anxiety disorders coexisting with alcoholism. A 12-week, double-blind trial involving 61 patients randomised to buspirone 20mg three times daily or placebo revealed significantly greater retention in the study, fewer drinking days at 6-month follow-up, and a trend to slower relapse for the treatment group.[124] A recent meta-analysis of buspirone in this population again showed increased treatment retention and improvements in anxiety.[125] A trial of buspirone in alcoholic patients not selected for a comorbid anxiety disorder failed to show an improvement in alcohol consumption, while still leading to significant improvements in several psychopathological measures.[138]

In patients with alcohol dependence, the lifetime prevalence of post-traumatic stress disorder (PTSD) has been shown to be 10% in men and 26% in women.[139] Nine such patients were treated with sertraline 200 mg/day for 12 weeks in an open-label fashion.[126] The results showed significant decreases in all 3 symptom clusters of PTSD, increased days of abstinence and decreased consumption at 3-month follow up. Limitations included the presence of other comorbid disorders such as depression in several patients, as well as a high dropout rate, with 3 noncompleters, 2 of whom were lost to follow-up. A large, controlled study is needed to confirm effectiveness.

Patients with antisocial personality disorder tend to be refractory to treatment, especially in the presence of other psychiatric disorders. 29 patients with antisocial personality disorder, alcohol dependence and a current affective or anxiety disorder had significantly fewer drinking days and increased abstinence rates following treatment with nortriptyline for 6 months.[128] No improvement was found for those who did not have a current affective or anxiety disorder.[128]

5.3 Bipolar Disorder

Of patients with bipolar affective disorder, 40% have an associated alcohol use disorder.[136] An open trial investigated valproic acid for 16 weeks in 9 patients with bipolar affective disorder and a concurrent substance dependence, 8 of whom used alcohol alone or in combination with other drugs.[129]

The trial showed significant improvements in both mania and depression, as well as decreased alcohol consumption at 6 months' follow-up. Finally, 2 case reports of patients with alcohol abuse, panic disorder and either bipolar or organic affective disorder described large improvements in alcohol use, panic attacks and affective episodes or instability when they were treated with valproic acid.[130] Controlled studies are needed.

6. Conclusions

There has been significant progress in the drug treatment of alcoholic patients. Recommended management of the alcoholic patient is summarised in figure 1. Given the many different medications that are discussed here, it is clear that no single pharmacological agent will be useful in all cases of alcohol dependence. Psychosocial modalities remain central to managing this illness, and in many of the trials involving pharmacological agents patients also received psychotherapy or other non-pharmacological interventions. Increasingly, however, adding medications to these other modalities is being shown to be effective in treating various components of the illness.

During an alcohol withdrawal syndrome, treatment with long-acting benzodiazepines, using a loading dose technique, has been shown to be a well tolerated and effective strategy. Once patients are abstinent, there is evidence to suggest that both naltrexone and acamprosate decrease consumption and help reduce relapse. If patients enter a comprehensive treatment programme, and do not have any contraindications to the medications, either naltrexone or acamprosate should be considered an integral component of their treatment plan. In patients with alcohol dependence and a comorbid psychiatric disorder, there is increasing evidence that pharmacotherapy is an effective tool. Specifically, antidepressants may be useful for a comorbid depression, and buspirone may be useful for chronic anxiety symptoms.

Further basic science and clinical research developments should produce more detailed infor-

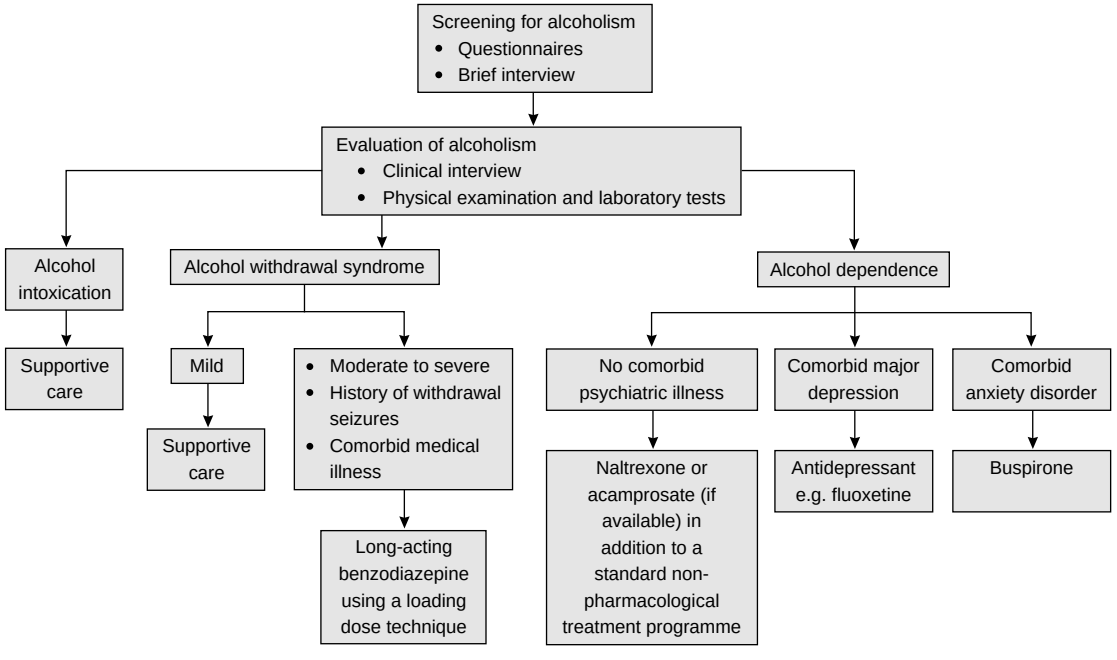

Fig. 1. Strategies for diagnosis and drug treatment of the alcoholic patient.

mation regarding the treatment of alcoholism, leading to improvements in the pharmacological strategies used in alcoholic patients.

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