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REVIEW

THE DRUG TREATMENT OF ALCOHOL WITHDRAWAL SYMPTOMS: A SYSTEMATIC REVIEW

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Abstract — A computer-assisted and cross-reference literature search identified trials of therapy for alcohol withdrawal symptoms. Those with a randomized, double-blind placebo-controlled design were systematically assessed for quality of methodology. Fourteen studies were identified investigating 12 different drugs. The quality of methodological design, even among this highly selected group of published studies, was often poor. Study populations were generally under-defined, most studies excluded severely ill patients, control groups were poorly matched, and the use of additional medication may have confounded results in some studies. Twelve different rating scales were used to assess severity of symptoms. All 12 compounds investigated were reported to be superior to placebo, but this has only been replicated for benzodiazepines and chlormethiazole. Further research using better methods is required to allow comparison of different drugs in the treatment of alcohol withdrawal symptoms. On the evidence available, a long-acting benzodiazepine should be the drug of first choice.

INTRODUCTION

Contemporary views on alcohol withdrawal symptoms have evolved since the work of Victor and Adams (1953) and Isbell *et al.* (1955). Victor and Adams (1953) described a series of alcohol-dependent patients admitted to a specialist unit in the USA. They identified the now well-recognized spectrum of symptoms, including: tremor, nausea, anxiety, tinnitus, muscle cramps, diaphoresis, seizures, hallucinations and delirium tremens, which comprise the alcohol withdrawal syndrome. Isbell *et al.* (1955) gave large quantities of alcohol to recently detoxified drug-dependent patients and described the symptoms they suffered when the alcohol was abruptly stopped. Alcohol withdrawal symptoms were later incorporated into the construct of the 'alcohol dependence syndrome' (Edwards *et al.*, 1981) and continue to be central to diagnostic classifications (e.g. World Health Organization, 1992).

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The onset of the alcohol withdrawal syndrome is most commonly gradual, but may be abrupt. Classically the milder symptoms appear within hours of cessation or reduction of alcohol consumption and subside over 2–7 days. Seizures may appear singly or as a series, usually within 24–48 h of alcohol withdrawal. Seizures are usually, but not always, preceded by other withdrawal symptoms (Saunders, 1987). Thirty per cent of patients who suffer fits may go on to develop delirium tremens (Victor, 1966). Delirium tremens most characteristically occurs after 48–72 h of alcohol withdrawal, is sometimes precipitated by additional stresses such as infection or head injury, and resolves over ~7 days. The proportion of drinkers affected by delirium tremens has been estimated to be as high as 5% in untreated withdrawal (Editorial, 1981) and may be experienced at some time by 12% of alcoholics (Schuckit, 1995).

Although the symptoms of the alcohol withdrawal syndrome are now well described, the underlying biochemical causes are still uncertain. It is not clear, for example, whether the with-

Table 1. Physiological changes in the acute alcohol withdrawal phase

Neurotransmitters
Raised: noradrenaline, acetylcholine, dopamine
Decreased: GABA, 5-HT
Receptor sensitivity
Increased: NMDA
Decreased: GABA
Endocrine
Raised antidiuretic hormone, aldosterone, corticotropin-releasing factor, growth hormone
Vitamins
Decreased: B_1, B_2, B_6, B_{12}, folic acid
Electrolytes and glucose
Low: H^+, Mg^{2+}, Ca^{2+}, Zn^{2+}, K^+, PO_4^{2-}, HCO_3^-, glucose

Adapted from Glue and Nutt (1990) and Lieber (1991).

drawal syndrome represents the various manifestations of a single process, or the common pathways of several abnormalities which commonly occur together. This uncertainty has been reflected in the treatments employed. It is now thought that chronic alcohol use causes alterations in several neurophysiological parameters to compensate for chronic central nervous system depression. Following cessation there is an overcorrection of these changes leading to withdrawal symptoms (Sellers and Kalant, 1976). Some of the physiological changes which have been described are shown in Table 1. The overall effect is that of rebound neuronal and biochemical overactivity following the prolonged depression of activity caused by alcohol. Disturbed electrolyte and vitamin levels may reflect poor dietary intake during the period of alcohol abuse.

TREATMENT OF ALCOHOL WITHDRAWAL

The treatment of alcohol withdrawal symptoms has tended to follow the prevailing theory as to their aetiology. Inevitably the great majority of alcohol withdrawal episodes occur with no medical supervision and the majority of medically supervised alcohol detoxifications occur in non-specialist settings, such as general medical and general psychiatry wards or, increasingly, at home (Shaw, 1995). Most episodes of alcohol withdrawal do not require sedative medication. Those individuals experiencing objectively observable withdrawal symptoms, and those with a past history of serious withdrawal symptoms, such as seizures or delirium tremens, are clearly in need of drug treatment, but criteria for predicting those cases which will benefit from medication have not been clearly defined, even among inpatients (Shaw, 1995).

The merits of any drug treatment need to be considered in the light of evidence for the effectiveness of non-pharmacological approaches. Whitfield *et al.* (1978) successfully treated 1024 of 1114 (91.8%) alcoholic inpatients without drugs. Staff, all college graduates, were 'given basic medical instruction' and trained to 'reassure and relate to disturbed alcoholics . . . restore familiar surroundings . . . be authoritative (to enable patients take control of their treatment)' within a specialist alcohol unit. Ninety patients (8.2%) were considered to be sufficiently 'seriously ill' to require medication and were sent on to a hospital. There was one case of delirium tremens and 12 seizures among the remaining 1024 patients. The mean inpatient stay was 8 days. On average, non-pharmacological treatment was required for only 2 days of the stay. The authors were unable to identify characteristics which distinguished the group requiring more intensive treatment before the development of seizures or delirium tremens. The major methodological weaknesses of the study were failure to: (1) use recognized diagnostic criteria; (2) define the study group adequately; (3) use a rating scale for severity of withdrawal symptoms; (4) define 'seriously ill'. The study is noteworthy for the

Table 2. Clinical trial quality rating scale

(a) Degree to which randomization was truly blind
(b) Inclusion of data from subjects who subsequently withdrew from the study
(c) Degree to which assessors were blind to the treatment allocation
(d) Whether subjects were assessed to determine if they had accurately guessed their treatment status
(e) Statement of criteria for improvement
(f) Use of multiple informants for assessment of outcome
(g) Method of determining dose of drug
(h) Whether concurrent treatment was held constant
(i) Length of baseline observation
(j) Control for previous treatment
(k) Control for co-morbidity

Adapted from Chalmers *et al.* (1981).

number of patients studied and the radical approach taken. The results suggest that placebo control groups are required in any evaluation of drug treatment efficacy if high-risk individuals are excluded.

The drug with the longest history of use and most widely used by drinkers for alleviation of withdrawal symptoms is alcohol itself. It has been estimated that >150 different drugs have been used to treat alcohol withdrawal symptoms during the past 30 years (Litten and Allen, 1991). Perhaps the most significant achievement of modern management of alcohol withdrawal has been to decrease the mortality from 15% in the 1960s (Victor, 1966) to <2% (Guthrie, 1989). However, factors other than advances in drug treatment, such as improvement in the overall health and nutritional status of Western populations, are likely to have been of equal or even greater significance.

This review of treatment research was conducted to update that carried out by Moscowitz *et al.* (1983), to determine whether or not more recent clinical research had learned from the methodological mistakes of the past and to see if clearer guidance could now be given on the most appropriate treatment of the alcohol withdrawal syndrome.

METHODS

A computer-assisted literature search (Medline) using key words (alcohol withdrawal, detoxification and treatment), plus manual cross-reference search of articles, review articles and contemporary text books, identified 51 trials of pharmacological treatment for alcohol withdrawal symptoms. Fourteen trials of double-blind placebo-controlled design were identified and scored for quality of design using a modified version of a scale developed by Chalmers *et al.* (1981). The scale comprises 11 aspects of study design and quality and is shown in Table 2. Each item is scored on a 4-point scale, 0 indicating that the paper failed to mention anything to enable that criterion to be rated, a score of three indicating a 'textbook' description of that criterion being satisfied. Only the source paper was scored, so that a study may score 0 on some criteria, because it referred only to a previous description of method with no further elaboration.

Twenty-two further comparison trials were identified that included at least one of the drugs that had been subjected to randomized, double-blind placebo-controlled studies. Although not analysed in depth, they are presented in the Results section. The remaining 15 trials were either open trials or comparison studies in which none of the compounds had been subjected to double-blind placebo-controlled studies. These are not described.

RESULTS

Table 3 describes briefly the 14 trials that were of a randomized, double-blind placebo-controlled design. Table 4 describes, more briefly, the 22 randomized, double-blind controlled trials which did not include a placebo group but which included one or more of the drugs which had also been investigated using a placebo-controlled design. The results show mainly efficacy data, as few trials published safety data to allow detailed comparison. The trials are grouped according to the drug being studied. Overall quality scores ranged from 8/33 to 22/33 (mean = 13.8). Studies with the highest quality designs generally had the smallest sample sizes.

Benzodiazepines

Benzodiazepine drugs are used as anxiolytics, hypnotics, premedication for surgery, muscle relaxants and anticonvulsants. Benzodiazepines act by potentiating GABA acivity and it is thought that their action in the withdrawal period is related to this effect.

Almost as soon as the prototypes were launched in the late 1950s and early 1960s, trials were performed to assess the efficacy of benzodiazepines in the treatment of alcohol withdrawal symptoms. One of the first large trials of chlordiazepoxide was published in the *British Medical Journal* in 1965 (Sereny and Kalant, 1965). On the basis of these early trials chlordiazepoxide and diazepam have become the favoured treatment in the USA and vie for the top position with chlormethiazole in Europe.

Diazepam was launched in 1961 and is the most widely used drug in Europe whereas chlordiazepoxide has been considered the drug of choice for alcohol withdrawal in the USA. The major differences are the superior anticonvulsant effect of diazepam and the claimed greater safety of

Table 3. Summary of randomized, double-blind and placebo-controlled trials of drugs in the treatment of the alcohol withdrawal syndrome

Study	Quality score	Drugs	Dose	No. of patients	Inclusion/exclusion criteria	Measurements	Additional medication	Results
Sereny and Kalent (1965)	16	Promazine Chlordiazepoxide	50/100 mg 25/50 mg	58	Male IP volunteer, no non-alcoholic organic lesions	Doctor's observation Tremometer Galvanometer	Only if DTs	4 fits with PZ & 1 DT, PZ = CDP for sleep, PZ decreased BP > CDP, CDP + PZ better than placebo
Sellers *et al* (1983)	10	Diazepam	20 mg/ 2-hourly	50	IP, CIWA > 20 No HI, OD, 'complex medical problems', allergy	CIWA-A hourly	Phenytoin if previous WD fits	DZ more effective than placebo, 90% required max. 9 doses, 56% placebo response
Burroughs *et al.* (1985)	17	Bromocriptine Chlordiazepoxide Chlormethiazole	7.5 mg 125 mg 4 g	71	>80 g of ethanol daily for >5 years IP <17 on Borg scale, 48 h no psychotropic medicine	SSA, Borg scale	CMZ if failed	Bromocriptine = placebo = 27%; vitamins improved; CDP = CMZ = best
Glatt *et al.* (1965)	18	Chlormethiazole	5 g	102	All admissions Nil specified	Doctor's 5-point and patient's 3-point global assessment, 82 Sx questionnaire not shown	Phenytoin and 10 mg CMZ if on placebo	CMZ quicker, 40% placebo response sedation in CMZ, doctor and patient noticed difference; higher initial neurological symptom score in placebo group
Bjorkqvist (1975)	8	Clonidine	0.15 mg	60	NS, consecutive self-referral on Monday/ Tuesday, 20–60 year male No chronic or severe acute medical illness	7-item 4-point scale Patient 38-item self-rating (not shown) Tremor measure	Phenytoin 'hypnotic' pm CPZ	Clonidine faster relief subjectively and required less chlorpromazine PZ Placebo group had higher previous history of fits
Wilkins *et al* (1983)	16	Clonidine	5 μg/kg	11	IP alcoholic, 3/6 WD symptoms; no Hx of fits, medical illness	Vital observations, TSA (own version)	Nil	Clonidine better relieving total symptom score and lowers ANS Sx anxiety (4 h cross-over study)
Sellers *et al.* (1977)	22	Propranolol Chlordiazepoxide CDP + PP	60/160 mg 100 mg 100 + 60 mg	30	Male 21–56, >160 g Ethanol daily >7 days, >80 g/day >2 years No medical illness or contraindication to medicines	34-item scale not shown, BP, pulse Tremometer	4 g ethanol per day for 1st 5 days, nil after	PP best for tremor, HR and BP Subjectively all = placebo All more effective than placebo on rating scale
Kraus *et al* (1985)	10	Atenolol	0–100 mg	120 per pulse	IP <24 h, 16–65 years No substance abuse, severe WD or contraindication to medication	9-item scale shown 4-point (3 subscales)	BZD	Atenolol = shorter in-patient stay and fewer sedatives required
Horwitz *et al* (1989)	7	Atenolol	As Kraus *et al.* (1985)	180	OP male/as Kraus No WD symptoms	Kraus 9-item scale craving VAS	Oxazepam	Atenolol decreased craving and ANS symptoms 37% failure rate on Atenolol Placebo group more previous DTs and fits, longer Hx of use
Bjorkqvist *et al* (1976)	9	Carbamazepine	800 mg	100	OP, 'seeking help cooperative', >3 day drinking No drug abuse, medical illness	15-item 3-point scale not shown, BP, HR Patient global VAS	Sedatives	64% of both groups successful CBZ faster relief; 18 drop-outs in both; 11 patients with side-effects in CPZ group

Sellers *et al* (1976)	19	Lithium	900 mg	18	Male, >160 g ethanol daily No liver disease, medical illness, contraindication to lithium or psychiatric illness	EEG, tremometer Motor tracking task 34-item scale + 17-item question Bloods	Nil	Lithium better than placebo in symptom relief subjectively
Borg and Weinholt (1982)	8	Bromocriptine	7.5 mg	60	Male 24–71 years, IP, 'gamma alcoholic' No exclusion specified	6-item 6-point scale FSCL, global assessment Blood prolactin	BZD, CBZ Dixyrazine	Bromocriptine relieved all symptoms 8 drop-outs Lower symptom score of bromocriptine group at start
Gallimberti *et al.* (1989)	13	GHBA	50 mg/kg	23	DSM-III WD No drug abuse, fits, DT, medical illness, epileptic treatment	6-item 4-point scale Word fluency	Nil	GHBA good but high rate of side-effects, especially dizziness, 7 h trial
Sampliner and Iber (1974)	15	Phenytoin	300 mg	157	History of fits Consecutive IP, 4 week constant intake No medical treatment	Questionnaire Presence of fits Bloods	CDP	No fits with phenytoin Fits early with placebo 11 in 11 patients

Key and abbreviations: =: equally effective; ANS = autonomic nervous system; Bloods: liver function tests, urea and electrolytes, and full blood count; BP = blood pressure; BZD = benzodiazepines; CBZ = carbamazepine; CDP = chlordiazepoxide; CIWA = Clinical Institute Withdrawal Assessment Scale; CMZ = chlormethiazole; CPZ = chlorpromazine; Dose: is the daily dosage of the drug unless otherwise specified; DT = delirium tremens; DZ = diazepam; EEG = electroencephalogram; FSCL = Fischer Symptom Check List; GHBA = gamma-hydroxybutyric acid; HI = head injury; HR = heart rate; Hx = past history; IP = inpatient; NS = no severe withdrawal at onset included; OD = overdose; OP = outpatient; PP = propranolol; PZ = promazine; prn = as required; SSA = selected severity scale; Sx = symptom; TSA = total severity assessment; VAS = visual analogue scale; WD = withdrawal.

Table 4. Studies in which one or more of the drugs has been investigated using a placebo control group

Study	Drugs	Measurements	Results
Chambers and Schulte (1965)	Diazepam Promazine	4-point scale (not shown)	Promazine = diazepam for DT and seizures Promazine better for mild symptoms
Goldbert *et al.* (1967)	Promazine Chlordiazepoxide Paraldehyde Alcohol	Own doctor's assessment (now shown)	Paraldehyde most effective Promazine least effective
Kaim *et al.* (1969)	Chlorpromazine Chlordiazepoxide Hydroxycine Thiamine	Nurses scale, mood scale, global rating scale, doctor's symptom scale (no scale shown)	Chlordiazepoxide best Chlorpromazine worst Most drop-outs with thiamine Seizures worst with chlorpromazine Mild symptoms all equally controlled Chlorpromazine least effect on major symptoms
McGrath (1975)	Chlormethiazole Chlordiazepoxide	Own 5-point scale (shown)	Chlormethiazole better Fewer drop-outs and fewer DT
Thompson *et al.* (1975)	Diazepam Paraldehyde	Not reported	Diazepam: quicker Paraldehyde: more untoward events
Palestine and Alatorre (1976)	Haloperidol Chlordiazepoxide	BPRS 5-point scale (not shown)	Haloperidol: better
Kramp and Rafaelsen (1979)	Diazepam Barbital	Doctor's and nursing observations	Oral barbital better for frank DT compared to i.m. diazepam
O'Brien *et al.* (1983)	Lorazepam Diazepam	TSA, global ratings	Lorazepam = diazepam One adverse event with lorazepam 11 drop-outs not evaluated
Wilson and Vulcano (1985)	Alprazolam Chlordiazepoxide	7-point semantic scale shown, Beck scale	Alprazolam = chlordiazepoxide More seizures in alprazolam group 3 DT in each group
Turbridey (1988)	Alprazolam Chlormethiazole	Doctor's and patients' ratings (not shown)	Alprazolam = chlormethiazole 1 seizure with alprazolam Chlormethiazole 10% drop-out group not evaluated
Kolin and Linnet (1981)	Alprazolam Diazepam	Doctor's and patients' global rating (not shown) HARS	Alprazolam = diazepam
Baumgartner and Rowan (1987)	Clonidine Chlordiazepoxide	Own alcohol withdrawal scale (not shown)	Clonidine more effective for autonomic symptoms and as effective for others
Madden *et al.* (1969)	Chlormethiazole Trifluoperazine	Own 2-point scale (not shown)	Chlormethiazole = trifluoperazine More anxiety in chlormethiazole group
Manhem *et al.* (1985)	Clonidine Chlormethiazole	Borg 4-point scale	Clonidine = chlormethiazole DT in both groups
Robinson *et al.* (1989)	Clonidine Chlormethiazole	Own scale (not shown)	Chlormethiazole more effective Higher drop-out rate for clonidine
Poutanen (1979)	Carbamazepine	Own scale (shown)	Carbamazepine effective for all symptoms. No seizures
Ritola and Malinen (1981)	Chlormethiazole Carbamazepine	Own scale (shown) VAS	Carbamazepine = chlormethiazole for symptoms More drop-outs with chlormethiazole More side-effects with carbamazepine

Table 4. *(continued)*

Study	Drugs	Measurements	Results
Agricola *et al.* (1982)	Carbamazepine Tiapride	3-point scale (not shown) VAS	Carbamazepine better Quicker for fear and hallucinations
Flygenring *et al.* (1984)	Carbamazepine Barbital	Own 5-point scale (shown)	Carbamazepine = barbital
Malcolm *et al.* (1989)	Oxazepam Carbamazepine	CIWA, BDI, global scale, anxiety inventory	Carbamazepine = oxazepam, including drop-out rate
Stuppaeck *et al.* (1992)	Oxazepam Carbamazepine	CIWA-A, global scale, self-rating scale	Carbamazepine = oxazepam for symptom relief days 1–5 Carbamazepine better days 6–7
Borg and Weinholt (1980)	Apomorphine Bromocriptine	6-point scale (shown)	Bromocriptine better after day 5 especially for tremor No side-effects

Key and abbreviations: =: equally effective; BDI = Beck Depressive Inventory, BPRS = brief psychiatric rating scale; CIWA = Clinical Institute Withdrawal Assessment Scale; DT = delirium tremens; HARS = Hamilton Anxiety Rating Scale; i.m. = intramuscular; TSA = total severity assessment; VAS = visual analogue scale.

chlordiazepoxide in overdose with alcohol (Serfaty and Masterton, 1993). Other differences include a longer half-life of diazepam (14–70 h compared to 4–29 h for chlordiazepoxide) and chlordiazepoxide causing less initial euphoria leading to a lower abuse potential. Other benzodiazepines which have been used for alcohol detoxification include oxazepam, lorazepam, alprazolam and flurazepam (Guthrie, 1989).

Chlordiazepoxide. There have been three double-blind, randomized placebo-controlled trials. All scored highly on the quality scale, but sample sizes were small, ranging from six to 20. Burroughs *et al.* (1985) found chlordiazepoxide to be equivalent in efficacy to chlormethiazole and superior to bromocriptine or placebo, for treatment of mild and severe symptoms. In a study of volunteers, chlordiazepoxide was as effective as promazine and more effective than placebo, in relieving mild withdrawal symptoms, but was less likely to be associated with seizures (Sereny and Kalant, 1965). Subjects developing delirium tremens prior to day 7 of the study were not included in the results. Sellers *et al.* (1977) found chlordiazepoxide to be inferior to propranolol but superior to placebo. The study groups comprised only six patients.

Diazepam. One randomized, double-blind placebo-controlled study has been made of diazepam. Sellers *et al.* (1983) treated 25 patients in moderate to severe alcohol withdrawal with 20 mg diazepam repeated 2-hourly until symptoms abated. All patients with a previous history of seizures were given additional anticonvulsants. Ninety per cent of the sample responded within nine doses of diazepam and required no further medication, the other 10% required 3–5 days of treatment. The apparent success of this short-term approach was thought to be due to the very long half-lives of diazepam and its metabolites. The placebo response rate was 56%.

Chlormethiazole

Chlormethiazole acts as a central nervous system depressant, causing sedation and sleep (Lundqvist, 1966). Chlormethiazole was first used in the treatment of delirium tremens during 1957 and introduced for milder symptoms in 1965 (Glatt *et al.*, 1965). Chlormethiazole is now a widespread treatment for inpatient withdrawal in Europe, but has never been licensed for use in the USA. Two randomized, double-blind placebo-controlled studies have shown chlormethiazole to be equivalent in efficacy to chlordiazepoxide (Burroughs *et al.*, 1985) and superior to placebo (Glatt *et al.*, 1965). Group sizes were 49 and 20 respectively. The patients in the Glatt *et al.* (1965) study were all given anticonvulsants. The placebo group had a lower initial severity of withdrawal symptoms and there was a 40% placebo response rate.

Clonidine

Clonidine is an alpha-2-adrenoceptor partial agonist and was first produced as a nasal decongestant but was subsequently found to have hypotensive properties. It was first studied in alcohol withdrawal because of the drug's known efficacy in opioid withdrawal states (Bjorkvist, 1975). In the Bjorkvist (1975) study, clonidine-treated patients' subjective ratings of withdrawal symptoms (other than sleep disturbance) resolved more quickly than the control group. Objective measures failed to show a significant difference. All patients were given additional sedation and anticonvulsants. The placebo group included more patients with a history of previous withdrawal seizures. A 6 h cross-over study, on a sample of 11 patients, found clonidine to control those symptoms thought to be due to sympathetic overactivity (tachycardia, hypertension, tremor, diaphoresis) more quickly than placebo following a single dose (Wilkins *et al.*, 1983).

Beta-blockers

Beta-blockers were first synthesized in 1958. Propranolol, the prototype drug, is non-selective, whereas atenolol is a specific beta-1-receptor blocker. Atenolol is thought to be safer in diabetics and unlike propranolol does not cross the blood–brain barrier. Beta-blockers are used in cardiovascular medicine and for controlling symptoms in phaeochromocytomas, hyperthyroidism and panic attacks. The use of beta-blockers in alcohol withdrawal was first proposed in the *Lancet* (Editorial, 1973) to treat symptoms due to autonomic nervous system dysfunction.

Propranolol. One randomized, double-blind and placebo-controlled trial has shown propranolol to be superior to chlordiazepoxide or a combination of both drugs in the treatment of mild withdrawal symptoms (Sellers *et al.*, 1977). Each sample group contained only six patients. Propranolol was subsequently reported to cause hallucinations, a known rare side-effect, more commonly when used in alcohol withdrawal treatment (Guthrie, 1989).

Atenolol

Two randomized, double-blind and placebo-controlled studies, using patient samples of > 100, have been published by the same centre in the USA (Kraus *et al.*, 1985; Horwitz *et al.*, 1989). Atenolol was used as an adjunctive treatment to benzodiazepines in mild withdrawal syndromes. The once-daily dosages were dependent on patient heart rate; no drug was given if the pulse was < 50 beats per minute (bpm), 50 mg if rates were 50–79 bpm and 100 mg if the pulse was > 80 bpm. Results suggested that the addition of atenolol shortened the length of inpatient stay, hastened improvement of symptoms and decreased the requirement for benzodiazepines (Kraus *et al.*, 1985). When used on an outpatient sample, patients on additional atenolol were less likely to drop-out of treatment and experienced less subjective craving for alcohol (Horwitz *et al.*, 1989). The apparent anticraving effect appeared to be limited to the withdrawal period. Whether the effects are similar for severe withdrawal phenomena has not been studied (Litten and Allen, 1991). The major criticism of both the American studies is the poor matching of the control groups for age, sex and alcohol consumption history. There was a high overall treatment failure rate in the Kraus *et al.* study. Seventy-two patients were excluded from analysis as they developed seizures, or 'combative or uncooperative states' during the withdrawal phase.

Anticonvulsants

Carbamazepine. The principal uses of carbamazepine are as an anticonvulsant, in chronic pain syndromes especially trigeminal neuralgia, and in the treatment of manic depressive psychosis. Carbamazepine acts on several neurotransmitter systems including GABA and noradrenaline, but its mechanism of action in the withdrawal state is uncertain. Carbamazepine was introduced in the 1960s and has been extensively used in Scandinavia for treatment of alcohol withdrawal states. Carbamazepine was first used in the treatment of delirium tremens in combination with sedatives in the early 1970s (Brune and Busch, 1971).

In the one double-blind, placebo-controlled trial (Bjorkvist *et al.*, 1976), a reducing dose of carbamazepine was given to 105 male outpatients. A hypnotic was also given. Results showed a significantly faster decrease in withdrawal symptoms in the carbamazepine group when compared with the placebo group. Despite one of the inclusion criteria being 'considered co-operative', there was a high drop-out rate, 18 patients from

each group. Eleven of the carbamazepine group suffered side-effects such as dizziness.

Phenytoin. In a randomized, double-blind placebo-controlled trial, Sampliner and Iber (1974) gave phenytoin 100 mg three times daily, in addition to unspecified chlordiazepoxide regimes, in the prevention of withdrawal seizures in 150 patients with a past history of fits. No seizures were seen in the 78 patients given phenytoin, whereas 11 of 77 patients given placebo suffered one seizure each.

It has been suggested that any anticonvulsant would exert a similar protective effect for the group of patients at high risk of fits (Saunders, 1987) and that in most cases a sufficiently high dose of a benzodiazepine or chlormethiazole is adequate to prevent seizures (Edwards, 1987).

Other drugs

Lithium. Sellers *et al.* (1976) postulated that lithium would lessen the activity of the sodium/potassium ATPase pump, which is increased in alcohol withdrawal. In a double-blind placebo-controlled trial on 18 patients with mild symptoms, nine patients who commenced lithium 0.3 mg three times daily prior to withdrawal had subjectively decreased symptoms. There was no change in objective measurements of tremor or vital signs in these patients. The effect was only present if treatment was commenced prior to abstaining from alcohol. No other treatment was given.

Bromocriptine. Alcohol is known to activate central dopamine, therefore possibly creating a period of dopamine receptor subsensitivity in the withdrawal period. Bromocriptine is a dopamine receptor agonist, primarily used in reproductive disorders, Parkinson's disease and acromegaly.

In a randomized, double-blind placebo-controlled trial, bromocriptine was found to have a significant effect on anxiety, restlessness, depression, tremor, nausea and sweating in withdrawal states, when compared with placebo (Borg and Weinholt, 1982). Interpretation of results is complicated by all patients having been prescribed benzodiazepines and carbamazepine, in varying doses, in addition to the study medication.

The therapeutic effect of bromocriptine was further questioned by Burroughs *et al.* (1985) who found it to be significantly inferior to chlormethiazole and chlordiazepoxide.

Gamma-hydroxybutyric acid. The most recent drug to be investigated in the treatment of alcohol withdrawal states is gamma-hydroxybutyric acid (GHBA). This is a normal constituent of mammal brain found especially in the hypothalamus and basal ganglia. It is thought to be a neurotransmitter, having its own specific receptor sites. It is used in the treatment of narcolepsy, as it decreases rapid eye movement (REM) sleep. It has been proposed that GHBA may be of use in withdrawal states because REM sleep is known to be increased. In a randomized, double-blind placebo-controlled study of 23 patients, GHBA was shown to decrease tremor, sweating, nausea, depression, anxiety and restlessness occurring during alcohol withdrawal in comparison with placebo (Gallimberti *et al.*, 1989). GHBA caused prominent side-effects, particularly 'dizziness', not further defined, which affected seven of the 11 GHBA-treated patients in the first 2 days of the trial.

DISCUSSION

Comparison of the randomized, double-blind placebo-controlled trials described in this paper is difficult due to methodological problems. Definition of alcohol dependence or abuse ranged from DSM-IIIR to Jellinek gamma type, whilst eight of the 14 studies simply used the term 'alcoholic' with no further elaboration. In addition to the possible diversity in sample selection that this implies, comparison is further hampered by the failure to use a single withdrawal symptom rating scale. Of the 14 scales used, only five had been previously published and each of these was used in only one of the 14 studies.

If the studies are difficult to compare, the methodological quality of most studies adds to the difficulties of the reviewer. Major failings in the studies were commonplace. Few papers recorded details of inclusion and exclusion criteria or revealed the proportion of the proposed study group thereby excluded. If 'severe' problems were excluded, severity was not clearly defined. Sample numbers were usually small. There was a general failure to consider or monitor treatment compliance, and to control for previous treatment or comorbidity. Complex drug regimes, in addition to the trial drug, including the use of drugs known to be effective in the treatment of alcohol withdrawal

symptoms, were common.

The clinical relevance of the studies is limited because seven of the 14 trials excluded 'severely ill' patients. It is possible that these authors considered any placebo treatment unethical for the severely ill, but the work of Whitfield *et al.* (1978), discussed earlier in this paper, the high response rates in placebo groups and the low incidence of delirium tremens and seizures in all studies suggest that there are means by which these reservations can and should be overcome.

The aims of drug treatment for the alcohol withdrawal syndrome are to enable the patient to stop drinking without psychological and physical morbidity or mortality. The effectiveness of any treatment may be measured against the extent to which it achieves these aims. The ideal drug treatment for the alcohol withdrawal syndrome should: (a) be effective against all withdrawal symptoms; (b) be effective as an anticonvulsant; (c) be effective in the prevention and treatment of delirium tremens and hallucinosis; (d) have a rapid onset of action; (e) have an easily adjusted dosage; (f) be available in oral and injectable forms; (g) prevent craving and minimize short-term relapse; (h) have a wide safety range; (i) have no side-effects; (j) have no interactions with alcohol; (k) not be liable to abuse.

The drugs described in this review have not been equally or systematically tested against most of these criteria. What follows is a summary of what can reasonably be extracted from the published literature.

Benzodiazepines are superior to placebo in the relief of alcohol withdrawal symptoms apart from hallucinosis, have a cleaner side-effect profile compared with all other drugs tested (Moscowitz *et al.*, 1983) and are safe in the high doses often required in delirium tremens (Woo and Greenblatt, 1979). Diazepam is available in oral, rectal and intravenous forms. The main disadvantage of the benzodiazepines is the risk of subsequent dependency, although this should be avoided if use is confined to the withdrawal period. Side-effects and interactions with other central nervous system depressants, particularly alcohol, which may rarely cause apnoea are more likely in the elderly. Care should also be taken when commencing treatment in those with hepatic impairment especially if using long-acting compounds. Seizures are more likely to occur with short-acting compounds (Hill and Williams, 1993).

Chlormethiazole is effective and is available in intravenous form for rapid sedation of acutely disturbed patients. A major disadvantage of chlormethiazole is its potentially lethal interaction with alcohol, causing respiratory depression and arrest (McInnes, 1987). This is particularly important to bear in mind for outpatients who may be at greater risk of drinking whilst on medication. Other potential problems include depression of the gag reflex (predisposing the patient to aspiration pneumonia) and confusion. As with benzodiazepines, dependency can be avoided by confining prescribing to the withdrawal period. However, concerns regarding the safety of chlormethiazole have led to the manufacturer advising outpatient use only in exceptional circumstances and the refusal to issue a safety licence for it in the USA by the Food and Drug Administration of that country.

Clonidine and atenolol are ineffective in preventing major withdrawal effects such as delirium tremens and have no anticonvulsant properties; they can only be considered as possible adjunctive treatments for the suppression of sympathetic nervous system overactivity (Brewer, 1995) and possibly in the reduction of craving during withdrawal.

Of the other drugs, carbamazepine may yet be demonstrated to have the most important role to play. The advantages of carbamazepine are that it is effective in severe alcohol withdrawal syndrome, including delirium tremens, and is well tolerated. Carbamazepine does not interact with alcohol, is not contraindicated in cirrhosis and may have an effect on the kindling process, thereby protecting against further withdrawal episodes (Ballenger and Post, 1984). Whether this last action is common to other anticonvulsants is not known. The disadvantages of carbamazepine are the potentially serious side-effects, including the small risk of potentially fatal haematological complications, and the higher relative cost compared to benzodiazepines. All other anticonvulsants share the risk of side-effects and it has been suggested that these agents may actually increase the incidence of seizures during withdrawal (Hillbom and Hjelm-Jager, 1984). None of the other new agents has proved to be superior to the older drugs. None is of proven use in severe withdrawal states, and all are much more

expensive.

With advances in neurophysiological and pharmacological knowledge, there are many new compounds that may prove to be useful in the treatment of alcohol withdrawal symptoms. However, future research will add substantially to current knowledge only if such research is properly conducted and described using: (1) recognized diagnostic criteria; (2) stated inclusion and exclusion criteria; (3) recognized, validated and reliable rating scales for withdrawal symptoms; (4) simple, clearly described, prescribing regimes; (5) sufficiently large sample sizes. Only with such studies will it be possible for new methods and existing methods to be properly compared, and integrated into clinical practice. In addition, further investigation into the biochemical and neurophysiological changes, that occur during alcohol dependence and withdrawal, is required to give a better understanding of drug action and to enable appropriate biochemical and neurophysiological measures to be used to monitor treatment of the withdrawal phase.

In their review of studies up to 1981, Moscowitz *et al.* (1983) concluded that the only consistent, statistically significant finding for mild to moderately ill patients was the superiority of benzodiazepines over placebo. The published evidence since then suggests that several drugs are probably effective against some alcohol withdrawal symptoms in some samples of drinkers. The most robust evidence remains for the use of adequate doses of a long-acting benzodiazepine, with due consideration given to the small additional risks in the elderly and those with liver disease.

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