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Trends in pharmacotherapy selection for the treatment of alcohol withdrawal in the Free State Province, South Africa

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Background. The selection of pharmacotherapy for the treatment of alcohol withdrawal remains a clinical challenge. Research continues into the underlying pathophysiology of dependence and withdrawal. A spectrum of clinical presentations of alcohol dependence is emerging, yet recommendations and guidelines have remained unchanged for some time.
Objectives. To engage with the problem of translating research into practice, as reflected by the selection of pharmacotherapy for alcohol withdrawal by medical practitioners in the Free State Province, South Africa.
Methods. A questionnaire-based survey and interviews were conducted among 121 professionals in both the private and public sectors across the province. A subgroup was formed comprising the 58 doctors who indicated that they prescribe for alcohol withdrawal. Participants worked in private general practice, specialist psychiatry practice, in a state hospital or in a treatment centre.
Results. Prescribing practices varied based on practitioners' geographical distribution and professional capacity. Deviation from standard recommendations included the routine use of clothiapine and antidepressants in withdrawal regimens. Prescribing clothiapine appears to be a local custom. While prescription of antidepressants may indicate unrealistic expectations of therapeutic benefit, there are clear indications that this is maintained to mask the diagnosis of an alcohol-related condition. Prescribing for alcohol withdrawal is therefore not necessarily determined by pathophysiology or efficacy of medication.
Conclusion. Withdrawal regimens need to be reassessed by researchers, policy makers and funders, balancing new developments with the real-life experiences and challenges of prescribers and their patients.

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New research is rapidly expanding the understanding of the pathophysiology of alcohol dependence.[1-4] While one might expect the role of pharmacotherapy in the treatment of alcohol withdrawal to develop parallel to these findings, translating basic research into clinical intervention is a lengthy process and by no means automatic.[5] Publications in medical journals and regional consensus guidelines allow information to flow from research to practice, yet it would be naïve to assume that formal research is the sole guide for clinical practice. It is prescribers who ultimately determine the selection of pharmacotherapy and therefore its actual role in treatment, and a range of factors may influence their decision-making process.

This study explored the prescription practices for alcohol withdrawal of medical practitioners in the Free State Province, South Africa. Comparing these practices with existing guidelines will help pinpoint areas that need attention in the translation process and identify expanded options that need to be substantiated by research.

The goal of pharmacotherapy in cases of alcohol withdrawal is to ensure safe and effective symptom relief and facilitate successful completion of detoxification, as an introduction to abstinence and rehabilitation. The main strategy for arriving at abstinence in safety and relative comfort is temporary substitution of alcohol with medication expressing cross-tolerance for alcohol, in particular long-acting benzodiazepines.[6-8] This enables the clinician to control the withdrawal process to some extent.

The development of alcohol dependence has been studied extensively. Beyond neuroadaptation, neuroplasticity contributes to the propensity for relapse.[4] Neurotoxicity follows both alcohol exposure and withdrawal.[2] The still unpredictable effect of adult neurogenesis during abstinence[1] further complicates the manifestations of the cycle of drinking, withdrawal, abstinence and relapse.

The development of Lesch's typology[3] demonstrates how hereditary and environmental factors play out in a clinical mosaic of expressions of alcohol dependence. Type 1 alcohol dependence (the model of allergy) is characterised by severe craving triggered by small exposures to alcohol.

In this type, rapid deterioration in the course of dependence has been linked to genetic factors involving methyl tetrahydrofolate reductase (MTHF) function, which may be amenable to intervention. Type 2 (model of anxiety) and Type 3 (model of depression) dependence may require more aggressive psychiatric and psychological intervention, while Type 4 (model of adaptation) dependence does not respond well to any intervention at all. Although interventions based on this typology[9] have not yet been widely accepted, the existence of the four types suggests that individualisation in the context of alcohol dependence might go beyond dose adjustments and the demands of treatment settings. Personalised drug selection, however, still lacks evidence-based support.

The therapeutic goals and the main strategy of alcohol detoxification have remained unchanged for some time. The evidence-based pharmacotherapy guidelines of the American Society of Addiction Medicine (ASAM),[8] the often-cited review of Kosten and O'Connor,[7] and recommendations specifically directed at family practitioners[9] unanimously support the substitution of alcohol with benzodiazepines, but do acknowledge potential alternatives such as carbamazepine and valproate.

Protocols can be individualised with fixed dosing, symptom-triggered dosing or loading doses with tapered titration, aimed at expediting withdrawal and decreasing the total dose of the medication. Asplund *et al.*[6] also propose modifications for the setting where withdrawal is undertaken.

Adjuncts such as beta-blockers, clonidine and calcium channel blockers are recommended when symptoms demand, and anti-convulsants when warranted by comorbidity.

Substitution requires supportive management with fluid, electrolyte and vitamin supplementation, magnesium and vitamin B combination products including thiamine. Asplund *et al.*[6] recommend that folic acid supplementation 'should be considered'.

This article describes the selection of pharmacotherapy for alcohol withdrawal – and the factors contributing to this selection – by prescribing health professionals in the Free State Province. These practices are compared with standard guidelines and explanations are sought for discrepancies in translation from research to clinical practice, through a survey and interviews. Finally, the meaning of these findings for the broader field of addiction medicine is discussed.

Methods

In this study, depictions of the treatment of alcohol withdrawal are based on descriptions by healthcare professionals directly involved in such cases. The study compiled geographically representative samples of general practitioners and state hospital practitioners through random selection, using randomisation tables as fully described by van Zyl *et al.*[10] The original sample comprised 77 general practitioners, 17 state hospital representatives, 11 private psychiatrists, three treatment centre representatives and 13 non-prescribing therapists. A subgroup was formed of the 58 participants who indicated during the original survey that they actually prescribe for alcohol withdrawal. Thus, for the purpose of this specific report, the response rate was 100%. The final group of prescribing participants consisted of 38 private general practitioners, eight state hospital representatives, 10 private psychiatrists and two treatment-centre representatives.

In this descriptive study, a questionnaire and semi-structured interviews were used to investigate the use of pharmacotherapy, as well as participants' perceptions and experiences regarding pharmacotherapy in alcohol withdrawal. These investigations were performed during face-to-face interviews between the first author and individual participants, which were recorded and transcribed. The preset themes used for the interviews included the participants' perceptions regarding their personal roles and the role of pharmacotherapy in treatment, perceived outcomes and enablers and deterrents for service delivery.

The interviewer used standard prods and paraphrasing to confirm understanding. NVivo 8 research software was used to perform content analysis of the qualitative data through text-based queries. Emerging themes were coded and clustered, followed by manual cleaning and cross-checking of data in relation to context.

On the questionnaire, participants indicated whether they used pharmacotherapy for alcohol withdrawal as 'standard therapy' (for all cases), '*pro re nata* (PRN)' (if specific symptoms arise), 'in selected cases' (for pre-withdrawal comorbidity) and 'do not use'. Field notes on the reasons for their selection were added. Quantitative data were analysed with the assistance of the University of the Free State Department of Biostatistics and are reflected as means and percentages.

The study did not investigate the individualisation of dosing regimens, or regimens based on the variation in interindividual manifestation of alcohol withdrawal as expressed in various typologies.

Although relatively small, the sample size was considered sufficient to give an indication of treatment trends in a range of contexts. It should be noted that treatment centre representatives, for instance, serve >100 patients for alcohol withdrawal per year, while individual general practitioners may treat <10 per year.

For the semi-structured interviews, individual sources were coded to preserve context without compromising anonymity. The codes used were: G = general practitioner; P = psychiatrist; T = treatment centre representative; and S = state hospital representative. For the purposes of state health service delivery, the province has been divided into Northern, Eastern and Southern health complexes.

Ethical approval to conduct the investigation was obtained from the Ethics Committee of the Faculty of Health Sciences at the University of the Free State.

Results

Selection of substitution agent for alcohol withdrawal

Table 1 shows the standard drugs used during withdrawal and the frequency with which they were prescribed. The selection of benzodiazepines v. clothiapine needs further elucidation. Table 2 shows the extent to which practitioners prescribe clothiapine in combination with or as a substitute for benzodiazepines. Clothiapine use was a geographical phenomenon, occurring more frequently among private general medical practitioners in the Northern Health Complex (Table 3).

Indications cited for clothiapine prescription included aggression (n=16), psychosis (n=2), severe withdrawal (n=1), agitation (n=3), restlessness (n=1), 'in the initial/acute phase' (n=2), 'in extraordinary cases' (n=1), delirium tremens (n=1) and for the patient 'to sleep' (n=1).

Participants who did not use clothiapine feared dangerous complications: the drug was 'not used due to side-effects' (n=2) or because it 'can cause convulsions' (n=2), while others warned

Table 1. Standard regimen of pharmacotherapy during alcohol withdrawal

	Number of clinicians prescribing various substitution drugs for alcohol withdrawal (*N*=58)			
Type of drug	As standard treatment, *n* (%)	In selected patients,* *n* (%)	PRN,† *n* (%)	Do not use, *n* (%)
Benzodiazepines	50 (86.2)	4 (6.9)	1 (1.7)	3 (5.2)
Clothiapine	18 (31.0)	14 (24.1)	10 (17.2)	16 (27.6)
Beta-blockers	5 (8.6)	8 (13.8)	7 (12.1)	36 (62.1)
Anticonvulsants	6 (10.3)	21 (36.2)	4 (6.9)	27 (46.6)
Antidepressants	14 (24.1)	12 (20.7)	2 (3.4)	33 (56.9)

*In selected patients: based on underlying comorbidity; †PRN (*pro re nata*): as required for symptoms appearing during treatment.

Table 2. Selection of benzodiazepines and/or clothiapine as a substitution agent for alcohol withdrawal by different professional groups

	Selection of pharmacotherapy for alcohol withdrawal		
Professional group	Benzodiazepine alone, *n* (%)	Clothiapine alone, *n* (%)	Benzodiazepine plus clothiapine, *n* (%)
General practitioners (*n*=38)	21 (55.3)	6 (15.8)	11 (28.9)
Private psychiatrists (*n*=10)	9 (90.0)	0 (0)	1 (10.0)
State hospital representatives (*n*=8)	6 (75.0)	0 (0)	2 (25.0)
Treatment centre representatives (*n*=2)	2 (100)	0 (0)	0 (0)
Total (*n*=58)	38 (65.5)	6 (10.3)	14 (24.1)

Table 3. Selection of clothiapine for substitution therapy among general practitioners in different geographical areas

	Frequency of prescribing clothiapine for alcohol withdrawal among general practitioners		
Geographical area	As standard treatment, *n* (%)	In selected patients* or PRN,† *n* (%)	Do not use, *n* (%)
Northern Health Complex (*n*=20)	12 (60.0)	7 (15.0)	1 (5.0)
Eastern Health Complex (*n*=10)	3 (30.0)	5 (50.0)	2 (20.0)
Southern Health Complex (*n*=8)	2 (25.0)	4 (50.0)	2 (25.0)
Total (*n*=38)	17 (44.7)	16 (42.1)	5 (13.2)

*In selected patients: based on underlying comorbidity; †PRN (*pro re nata*): as required for symptoms appearing during treatment.

Table 4. Routine prescription of antidepressants by different professional groups during alcohol withdrawal

	Frequency of prescribing antidepressants for alcohol withdrawal		
Professional group	As standard treatment, *n* (%)	In selected patients* or PRN,† *n* (%)	Do not use, *n* (%)
General practitioners (*n*=38)	6 (15.8)	13 (34.2)	19 (50.0)
Private psychiatrists (*n*=10)	2 (20.0)	3 (30.0)	5 (50.0)
State hospital representatives (*n*=8)	1 (12.5)	1 (12.5)	6 (75.0)
Treatment centre representatives (*n*=2)	1 (50.0)	1 (50.0)	0 (0)
Total (*n*=58)	10 (17.3)	18 (31.0)	30 (51.7)

*In selected patients: based on underlying comorbidity; †PRN (*pro re nata*): as required for symptoms appearing during treatment.

that 'death can occur with intra-arterial administration' (*n*=1), and clothiapine 'should have no place in treatment' (*n*=1).

The use of antidepressants during alcohol withdrawal

Table 4 shows that 17.3% of respondents routinely prescribed antidepressants as standard therapy during withdrawal of alcohol. One reason for this practice was that a diagnosis of major depression means that medical schemes will pay for treatment and allow patients to be admitted to hospital (*n*=4). Respondents said:

- 'As long as you put it through as depression. You don't ever write "alcohol" when it comes to the medical aids because they will not pay for any treatment or medication. So you always write depression.' (General practitioner, Northern Health Complex)
- 'Look, there we have the hospital: it is relatively comfortable. Maybe we do bend the rules a little with the specific diagnosis to get the person admitted and then we have to work carefully with the medication as well so that the medical scheme does not refuse to pay for the person.' (General practitioner, Eastern Health Complex; translated from Afrikaans)
- '(I) often help [patients] without funding, or by admission under another diagnosis.' (General practitioner, Southern Health Complex; translated from Afrikaans).

Psychiatrists were adamant that they treated only dual diagnosis patients: '[I] cannot admit the patient purely for withdrawal … must admit if there is depression, etc.' (Psychiatrist, Southern Health Complex; translated from Afrikaans)

The use of anticonvulsants during alcohol withdrawal

Anticonvulsants were used almost exclusively in patients with an existing history of convulsions (Table 5). Respondents used carbamazepine in patients with previous withdrawals complicated by delirium tremens (*n*=2) or seizures (*n*=3), concurrent mood disorders (*n*=1), epilepsy (*n*=2) or cardiomyopathy (*n*=1). Carbamazepine was also prescribed when the current withdrawal process was severe (*n*=1), or complicated by seizures (*n*=4) or delirium tremens (*n*=4). 'Longstanding alcohol addiction', 'complicated cases', 'irritable patients' (all *n*=1) and 'heavy drinkers' (*n*=2) were all listed as warranting carbamazepine.

Table 5. Use of anticonvulsants in alcohol withdrawal

Type of drug	Frequency of prescribing anticonvulsants for alcohol withdrawal (*N*=58)		
	As standard treatment, *n* (%)	In selected patients* or PRN,† *n* (%)	Do not use, *n* (%)
Carbamazepine	3 (5.2)	18 (31.0)	37 (63.8)
Phenytoin	3 (5.2)	2 (3.4)	53 (91.4)
Valproate	1 (1.7)	5 (8.6)	52 (89.7)

*In selected patients: based on underlying comorbidity; †PRN (*pro re nata*): as required for symptoms appearing during treatment.

Table 6. Prescription of vitamin and mineral supplementation during alcohol withdrawal

Supplement	Frequency of prescribing supplements for alcohol withdrawal (*N*=58)	
	As standard treatment, *n* (%)	Not part of standard regimen, *n* (%)
Vitamin B complex	54 (93.1)	4 (6.9)
Thiamine	18 (31.0)	40 (69.0)
Magnesium	8 (13.8)	50 (86.2)
Folic acid	1 (1.7)	57 (98.3)

Selected cases would receive barbiturates for concurrent epilepsy (*n*=1), agitation (*n*=2) 'symptomatic relief of headache' (*n*=1); anxiety (*n*=2); 'polysubstances' (*n*=1) or a 'history of convulsions' (*n*=1).

Valproate was used in selected cases for mood disorders (*n*=2), epilepsy (*n*=3), if a patient convulsed (*n*=3), 'if expecting complications' (*n*=2) and in 'irritable patients' (*n*=1).

Indications for phenytoin were 'high risk patients' (*n*=1) and convulsions (*n*=1). Three participants included prophylactic phenytoin in their standard regimen.

Vitamins and minerals

Table 6 shows the use of vitamin and mineral supplements in alcohol withdrawal regimens. Fifteen participants (25.9%) indicated that they combined thiamine with vitamin B complex.

Discussion

The majority of participants routinely prescribed benzodiazepines during withdrawal, consistent with the standard method of treatment.[6-8] Long-acting benzodiazepines replace alcohol effects and counteract the relative excess of excitatory neurotransmitters during withdrawal. The gamma-aminobutyric acid (GABA)-enhancing action offers symptomatic relief, is neuroprotective[11] and has been shown to prevent the progression of seizures over repeated episodes of withdrawal (so-called 'kindling', in which consecutive episodes progressively become more severe).[12]

Though the use of neuroleptic drugs in alcohol withdrawal is not uncommon, it may be argued that the use of clothiapine is misplaced in a routine regimen. Neuroleptic drugs reduce withdrawal symptoms, but are less effective than benzodiazepines. They also have a less favourable side-effect profile, including extrapyramidal symptoms, orthostatic hypotension and anticholinergic effects. Dopamine antagonism may aggravate withdrawal symptoms, delirium and seizures, while neuroleptic malignant syndrome increases mortality. The use of antipsychotics is argued to be detrimental for craving in Lesch Type I patients.[9]

Mayo-Smith *et al.*[8] proposed that neuroleptics can be used as an adjunct to benzodiazepines, but not in place thereof. The combination of benzodiazepines and antipsychotics increases the risk of respiratory depression.

However, all of these reports have considered neuroleptics as a group, and clothiapine has not been considered individually and in terms of its unique characteristics. Its main advantage is its effectiveness in calming agitated patients. Though the drug is registered for alcohol withdrawal, the South African Medicines Formulary[13] warns that it is contraindicated in alcohol intoxication and in patients prone to convulsions. Limited evidence, dating from the early 1980s, is available regarding its efficacy for suppressing alcohol withdrawal symptoms with good compliance, low incidence of side-effects and lack of craving.[14]

The drug, however, has not featured in the major recommendations. The unanswered question is whether clothiapine has a positive or negative influence on the long-term course of a particular case.

Routine use of antidepressants during withdrawal is unorthodox. According to DSM-IV criteria,[15] a dual diagnosis can only be made when the symptoms of depression persist after one week post-withdrawal. Several general practitioners openly admitted that the prescription of antidepressants was not for therapeutic purposes, but to mask the true diagnosis from medical schemes in order to ensure continued payment for admission, medication and services.

The Medical Schemes Act[16] provides for prescribed minimum benefits (PMB), a package of acute life-threatening conditions that medical schemes have to cover. Withdrawal states are included in the PMB, yet addiction is not listed under the list of chronic conditions. Some medical schemes specifically indicate that addiction is excluded from benefits or argue that self-induced conditions are justifiably excluded.

Withholding information from a medical scheme is unlawful in South Africa, yet service providers clearly see this as the lesser evil when the alternative is non-treatment. There is also a general mistrust of medical schemes and the extent to which they will pay for PMB, and the real fear that disclosure of a specific condition, such as alcohol dependence, will jeopardise payment for current and future claims. This situation points to a need for open and honest discussion between health service providers, hospitals and medical schemes.

Could antidepressants, however, hold some clinical advantage? A meta-analysis by Nunes and Levin[17] showed that the beneficial effects of antidepressant therapy on substance use are related to its effects on depression, yet rates of sustained alcohol abstinence were low. Double-blind, placebo-controlled studies on the effect of serotonin re-uptake inhibition on abstinence showed a decrease in alcohol intake and, in some cases, a significant increase in the number of abstinent days. These effects, however, were seen in small samples and short-lived. In the absence of depression, the effects on alcohol consumption are inconsistent. In

fact, worsening outcomes have been described in patients with more severe alcohol dependency.[17]

The routine use of vitamin B complex during withdrawal is found in all standard recommendations. Combined administration of vitamin B_1, B_2, nicotinamide, B_6 and pantothenic acid is essential, as single administration of thiamine and nicotinamide may lead to a relative deficiency of other B vitamins. Additional thiamine supplementation is often prescribed to prevent acute beri-beri. The literature on supplementation emphasises maintaining stable blood glucose levels, regulating fatty acid redistribution and addressing vitamin deficiencies.[6-8] Folic acid supplementation is particularly relevant in Lesch Type I patients, whose high homocysteine levels contribute to the severity of the withdrawal and the long-term development of their dependence.[18,19] Again, supplementing folic acid in isolation may be detrimental, triggering acute neurological symptoms due to vitamin B_{12} deficiency. Long-term folic acid has also been implicated in accelerating carcinogenesis.[20]

In current consensus and expert guidelines, therapeutic goals for alcohol withdrawal are limited to short-term safety and relief of withdrawal symptoms. In practice, however, the selection of pharmacotherapy is influenced by local custom, personal prescribing habits, the availability of medication, and hospital and funding sources' policies. Research into the underlying pathophysiology of alcohol dependence suggests that long-term outcomes may be affected by the management of withdrawal. This implies an urgent need to rethink therapeutic goals and redefine relevant outcomes for pharmacotherapy research.

A long-term outlook needs to be fostered, rather than episodic intervention. Given the evidence of the neurotoxic nature of withdrawal and the kindling effect of repeated withdrawals,[21] the relative neuroprotective features of drugs used in withdrawal is crucial. Similarly, the role of aggressive treatment of episodes in delaying the onset on early withdrawal seizures, must be investigated.[12]

To select agents to treat withdrawal, prescribers must consider expected long-term effects, not only the immediate relief of symptoms. They should also focus on the effects on primary neuropathological processes, such as neurotoxicity v. neuroprotection, reversal of neuroplastic events, and the prevention of kindling as reflected in the progression of craving, seizure threshold and withdrawal symptoms.

Research shows that variations in patients' clinical presentation should have a much more profound effect on the way we approach withdrawal. Treatment individualisation needs to be expanded, beyond adapting dosing schedules to reduce the total dose of benzodiazepines used or for the treatment setting.

Conclusion

This study demonstrates the need for comparative studies on the efficacy of drugs in homogenous patient groups, to ensure not only that best practice survives, but that alternatives are duly investigated. Furthermore, discourse between research and clinical practice is necessary to identify and overcome obstacles in translating findings into practice. The role of policy makers (including that of professional bodies and interest groups) in facilitating or undermining translation should not be underestimated, and must be accounted for in overall strategic planning.[22,23]

Pharmacotherapy for alcohol dependence can only reach its full potential if used to influence the pathophysiology of the process, rather than for mere short-term symptomatic relief. Therefore, treatment regimens must be re-evaluated in the light of emerging biological evidence. If the withdrawal process itself contributes to the progression of the disease, preventing complications thereof should be of the utmost importance. If there is a variation in expression of the condition, it has to be reflected in the selection of treatment.

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