Baclofen for alcoholism

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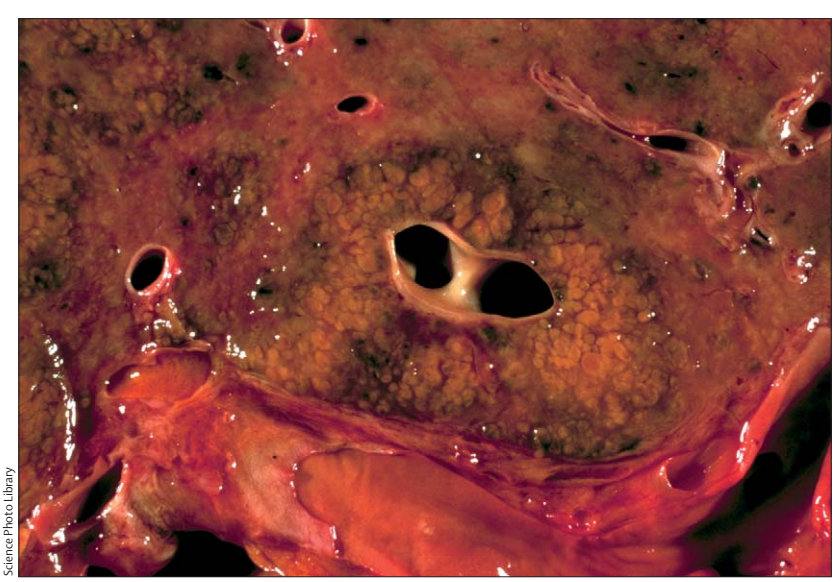
In today's *Lancet*, Giovanni Addolorato and colleagues[1] report the first randomised placebo-controlled trial of a treatment for alcoholic patients with cirrhosis of the liver. Their finding that baclofen, a $GABA_B$-receptor agonist, was better than placebo for reduction of drinking in such patients is of interest both because of its specific results and because it highlights the broader context of drug treatment for alcoholism.

Patients with alcohol-related liver cirrhosis who are actively drinking present complex problems for clinical management. Cessation of alcohol consumption or significant reductions in alcohol use improve survival in alcoholic liver disease[2]—an important goal given that chronic liver disease and cirrhosis were the 12th leading causes of death in the USA in 2004, with 26 549 deaths.[3] However, achievement of abstinence or significant reductions in drinking in these patients can be difficult.

Pharmacotherapy for alcoholism is undergoing a period of growth and scientific excitement. Three new treatments for alcoholism (oral and long-acting intramuscular naltrexone, and acamprosate), have received regulatory approval. Unlike disulfiram, these preparations target neurobiological processes that are thought to be involved in the pathophysiology of alcoholism. Overall efficacy is modest, although for some patients the clinical effects seem robust. Patients with cirrhosis have been excluded from trials of these drugs partly because of fear of drug-induced hepatotoxicity (with naltrexone) or, more generally, a concern about overall medical stability secondary to impaired liver function.



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Liver cirrhosis

Addolorato and colleagues found that baclofen, in 42 alcoholic patients with cirrhosis compared with 42 such patients given placebo, improved rates of total abstinence (71% *vs* 29%, odds ratio 6·25, 95% CI 2·4–16·1), increased the percentage of non-drinking days (63 days *vs* 31), and reduced relapse to heavy drinking at 60 days (19% *vs* 45%). Importantly, no hepatotoxicity or other serious side-effects were noted in patients receiving baclofen. Baclofen was selected for study on the basis of its preliminary evidence of efficacy for alcoholism,[4] and the fact that it is not metabolised by the liver and is not hepatotoxic. Participants were recruited from consecutive referrals to the investigators' clinic, which specialises in the management of liver disorders and alcoholism. Participants were required to be actively drinking but none was excluded for not meeting this criterion, which indicates that this population might have been referred because of its recalcitrance about treatment for alcoholism. 43% of potential participants were excluded from enrolment mainly because of medical conditions, but only 3% refused to participate—which is unusual for a clinical trial recruiting consecutively.

Addolorato and colleagues' results are surprisingly robust in favour of baclofen, with nearly three-quarters of patients on baclofen maintaining sobriety compared with about a quarter of placebo patients. More patients assigned to placebo dropped out (31%) compared with baclofen (14%) and, because dropouts were counted as failures in the sobriety survival analysis, they will have affected the primary outcome measure. However, the higher retention rate in the baclofen group is of interest in its own right. Additionally, completer analyses, in which dropout data were not analysed, showed baclofen to be better than placebo, which lends support to the primary hypothesis. The length of the study was relatively brief, 12 weeks of active treatment plus 4 weeks of follow-up, and it will be important to study patients for longer periods to understand the durability of this intervention. Of course, replication of the findings will be necessary in other populations with varying inclusion and exclusion criteria and with

different methods of recruitment to assess whether baclofen has true value in patients with cirrhosis who continue to drink. Nevertheless, the findings are welcome because they could spur further efforts to identify drug treatments for alcoholism complicated by cirrhosis.

Addolorato and colleagues' study should also be viewed in the broader context of the use of pharmacotherapy for alcoholism. Two points are worth mentioning. First, most drug trials for alcoholism exclude severely ill patients with alcoholism, including those with medical, psychiatric, and comorbid substance misuse problems. Such exclusion is done to improve the homogeneity of the sample population, enhance retention, reduce drug–drug interaction, and minimise adverse events. Although these goals are laudable, one consequence is that external validity is reduced. Alcoholic populations have important medical comorbidities, and substantial comorbid psychiatric problems (37%)[5] and other substance misuse disorders (29–35%).[6] Clearly, interventions are needed for these populations and appropriate clinical trials are essential.

The second broad point is that despite the scientific success of discovering effective drugs for alcoholism, use of these medications by clinicians has lagged. The findings of modern clinical trials, such as the one reported by Addolorato and colleagues, should be transferred to primary care settings if these treatments are to substantially affect public health.

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We declare that we have no conflict of interest.

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A wake-up call for global access to salvage HIV drug regimens

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For HIV-infected populations fortunate enough to access treatment, combination antiretroviral therapy (cART) profoundly reduces mortality. A wide variety of antiretrovirals have been developed in the past decade, but few are accessible to most patients in developing countries. In such settings, only one or two regimens are normally available, which results in disastrous consequences when these regimens fail. The success of first-line therapy for these populations is of pressing concern.

In today's *Lancet*, Andrew Phillips and colleagues report on a UK cohort of patients with low rates of triple-class drug failure,[1] especially those starting therapy with CD4 counts greater than 200 per µL. The good news is that few patients had extensive drug failure. The bad news is that of those patients with extensive drug failure, most had failed more than seven drugs and a large proportion of those (58%) failed second-line therapies. This finding has implications for the treatment of patients in developing settings, where access to multiple drugs within classes are limited and resistance testing and viral load evaluations are luxuries outside the realm of routine clinical care.

African patients differ somewhat from the UK cohort in terms of CD4 counts at start of cART, prevalence and type of co-infections, levels of nutrition, and availability and frequency of virological monitoring.[2] UK patients that began cART with CD4 counts below 200 per µL were more likely to fail therapy, according to Phillips and colleagues, yet that is the upper boundary for starting most patients in developing settings. Perhaps more importantly, in developing countries cART generally consists of one non-nucleoside reverse-transcriptase inhibitor (NNRTI) plus two nucleoside reverse-transcriptase inhibitors (NRTI); second-line therapies, ritonavir-boosted protease inhibitors, and beyond are often unavailable.[2] Whereas Phillips and colleagues could assess virological outcomes, assessment of cART effectiveness in most