

CLINICAL CONTROVERSY SERIES

Are Medications that Reduce Risk of Drinking or Heavy Drinking, or that Promote Abstinence, of Value in the Treatment of Alcohol Dependence?

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NEGATIVE VIEWPOINT: STUART GITLOW, MD, MPH, MBA

Years of effort in the field of alcoholism have led to a well-characterized and defined illness in which quantity and frequency of alcohol use is not a factor.¹ Longitudinal studies suggest that this disease entity is present prior to the first drink, and that alcohol intake is merely a marker for the presence of the illness.² Some of us, rather than studying alcoholism, choose to study alcohol dependence as defined within DSM-IV. A rigid application of DSM criteria suggests that alcohol dependence dissipates once the specific criteria are no longer met, even if a patient continues to actively drink. Those strictly applying DSM criteria can therefore proclaim success where those studying alcoholism would perceive failure. Thus, the first response to this question must reflect the concern that the research of alcohol dependence might not be applicable to those suffering from alcoholism.

Fortunately, the definitions of alcohol dependence and alcoholism agree on quantity and frequency of alcohol intake as being irrelevant. One can drink comparatively little and infrequently yet still suffer from either disease. To determine if medications that alter alcohol intake have value in treating alcoholism, researchers and readers must keep in mind these

points, which happily apply just as well to the DSM-defined alcohol dependence:

- We know that morbidity and mortality vary with respect to alcohol intake in the general population, but we do not have a curve available for alcohol intake versus morbidity/mortality within a group of those with alcoholism. The two curves might look very different. Decreases in alcohol intake short of abstinence, besides being irrelevant to diagnosis, may have no bearing upon disease course or morbidity/mortality. Reduction in the percentage of days on which a patient drinks heavily, as an outcome measure, ignores a potential overall increase of alcohol intake. Even without such an increase, there is no evidence to suggest that altering this outcome measure results in real improvement *in alcoholics*. We need our outcome measures to be chosen based upon their value to those with this disease, where value is the degree to which we observe decreased complications accompanied by improved overall function.
- Studies that confine their inclusion criteria to those who drink heavily and regularly^{3,4} or to those who have had a fixed period of sobriety⁵ limit the applicability of their conclusions to only those subsets, often a minority of those with the disease in question. As a result, such studies cannot be broadly interpreted as applying to all patients with the disease but only to the fraction of those who fall into the inclusion group.
- Study subjects must have their alcohol intake measured objectively without reliance upon self-reported information. Similarly, studies must not ignore the host of cross-tolerant medications subjects may be

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taking, including benzodiazepines, barbiturates, non-benzodiazepine sedatives, and carisoprodol, whether prescribed or not. Given that alcoholism is a subcategory within the broader context of sedative dependence, the use of any of the cross-tolerant substances can lead to uninterpretable study results. If a study subject has decreased alcohol intake—a result of questionable utility in itself—but increased diazepam intake concurrently, how should we score this outcome? That would be similar to a subject decreasing hard liquor and increasing beer intake, would it not?

- Medication recipients must be compared to a control group receiving gold standard treatment. The best reported treatment efficacy has been achieved with physicians providing treatment—not simply the provision of medications, but the entirety of medical treatment.^{6,7} If 70% of patients achieve abstinence at one year when treated by physicians, but only 30% achieve abstinence when receiving other forms of therapy, is a 40% rate achieved with use of medication a success or failure?
- Because alcoholism is a lifelong illness, short-term alterations of alcohol intake are of questionable importance in light of the fact that recovery can be achieved with proper treatment. Mere abstinence can be achieved by placing an individual in confinement, but this has little impact upon disease progression as subjects quickly return to original symptoms upon release. One might suspect that a short-term reduction of use is beneficial as it provides an opportunity for treatment of the underlying disease. We do not know, however, if an imposition of reduced use, whether imposed by confinement or by medication, alters the degree to which a patient might be receptive to treatment from that present if they have reduced or discontinued use secondary to free will while in treatment.

Any hypothetical drug that reduces the risk of heavy drinking might have great value for heavy drinkers, given the potential for resulting medical complications. Our alcoholic patients may not obtain the same value. Feeling the medication represents treatment, yet continuing to drink, our patients would remain at high risk of complications of their disease (only some of which are the result of the alcohol use per se). Perhaps these medications hinder the patients from obtaining gold standard abstinence-based treatment that would result in better odds of long-term health. Perhaps they lead the patient to obtain medically monitored treatment instead of real medical healthcare, which we know has excellent results in treatment of addiction. Perhaps the medicine prevents the alcoholic from being receptive to treatment that would have actually led to recovery.

Thus, we must first take a group of patients with alcoholism that represent a cross-section of those with the disease, and then demonstrate that our outcome measure is of long-term

value, all while making sure that other cross-tolerant drugs are not interfering with our measurements. We then must indicate that a medication produces this useful outcome at a higher rate than that obtained with gold-standard medical care, and finally indicate that the long-term results of such treatment are at least as good as that obtained with gold-standard care. Once we've done that, then such medicines can be considered as part of our regimen for those with this lifelong illness. Until then, we remain uncertain as to whether these drugs are useful or harmful with respect to treatment of alcoholism; they therefore remain experimental, FDA indications notwithstanding.

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AFFIRMATIVE VIEWPOINT: MARK L. WILLENBRING, MD

In the treatment of alcohol dependence, the primary focus of medication development has been to reduce relapse during early recovery among people who either are abstinent or who desire to be. It is irrefutable that available published evidence supports the efficacy of several different medications to accomplish this goal.^{1–3} To assert that medications are not useful, then, necessarily requires one of the following arguments:

1. one cannot use the scientific method to study recovery from alcohol dependence because it is not amenable to scientific study (for example, because it is a spiritual process that cannot be measured empirically),
2. the studies that have been conducted are fundamentally flawed and the conclusions are therefore erroneous, or
3. the findings from these studies are technically correct but are not clinically meaningful or important, so they are irrelevant to the clinician (and patient).

The first assertion is perhaps the most straightforward and cannot be refuted, because it requires a priori assumptions about the nature of human life, cosmology, and philosophy that

are at variance with science. On the other hand, this assertion also cannot be proven, for the same reason. If one rejects the scientific method, then how can we determine comparative efficacy of different treatments, except for competing unverifiable opinions? This answer contradicts the growing emphasis on empiricism that characterizes addiction psychiatry and is probably not a relevant topic for consideration here.

Turning now to the next question of whether the studies conducted to date are fundamentally flawed, there are many potential objections one might raise about methodology. No study is perfect, and understanding the shortcomings and compromises of any particular study provides an important context within which to interpret study findings. For this reason, the results from a particular study are usually not considered definitive. Replication of study findings, particularly by different investigators, reduces the probability that the first study results were a chance finding or biased result. Meta-analysis of the findings from many randomized trials has become one standard to determine overall efficacy of a certain treatment. Sometimes a large, thorough, randomized controlled trial is considered confirmatory or definitive.⁴ For both naltrexone and acamprosate, multiple meta-analyses have concluded that they are effective at either reducing relapse or prolonging abstinence,^{1–3} and naltrexone's efficacy has been confirmed by a very large multi-site trial.⁵ Topiramate's efficacy has been established by a well-done, randomized controlled trial with confirmation by a large multi-site trial.^{6,7} By all current scientific standards, then, these medications have proven efficacy.

Thus, to disregard this entire body of pharmacotherapy research would require the identification of more fundamental flaws than simply whether a particular randomization worked as planned, or whether specific inclusion and exclusion criteria were used. In fact, one would have to argue that fundamental concepts used to study a disorder are wrong. For example, one could argue that the definition of alcohol dependence used in these studies is completely wrong, so whatever the studies reveal, they are not addressing *true* alcohol dependence. Another example would be that the outcome measures used are all so biased or imprecise that they do not truly represent the variables they are attempting to measure, or that the wrong outcomes are being measured.

The methodology for conducting treatment efficacy trials in alcohol dependence has improved markedly in the past twenty years. Hundreds of investigators have worked to refine and standardize study procedures. Funding agencies and review groups, scores of journal reviewers and editors, and independent bodies such as the Cochrane Collaboration agree on the fundamental approach taken in these studies. Further, an international consensus exists as to the essential components of the alcohol dependence syndrome.^{8,9} Although refinements continue to be made, especially in data analysis and study design, there has been no serious challenge to the basic methods of study that are used. To the contrary, these methods are broadly accepted across biomedical research. It has been conclusively demonstrated that medications significantly

reduce heavy drinking and/or increase abstinence during early recovery. Because morbidity and mortality are closely tied to heavy drinking and to disability, how can these results not be regarded as important?

The final assertion to be considered is whether the treatment effects associated with medications are too small to be meaningful or that reducing relapse in early recovery does not have value, or that they do not generalize to real-world patients who often have conditions that would exclude them from research trials. To state that a treatment has a small or moderate effect is not the same as saying that it has *no* effect, merely that it is not as large or robust as we would like to see. It is not unusual, for example, for some studies to be positive and some to be negative when the real effect size is small to moderate. (Note: "effect size" is a specific technical term used to compare studies in meta-analysis. It is not the same as "clinical effect.") Meta-analysis is used to estimate effects across many studies, and several meta-analyses have confirmed the efficacy of these medications. Overall, the clinical effect of these medications has been to reduce early relapse by 20–40%. Relapse is not only destructive in itself, but early relapse often leads to an overall poor course. For example, in the COMBINE trial, compared to those taking placebo and receiving brief medical support only, subjects taking naltrexone were about twice as likely to have a good clinical outcome at the end of 16 weeks of treatment.⁵ Therefore, unless there are offsetting adverse effects, it seems obvious that prevention of even one relapse is inherently a good thing.

An unresolved question is whether reduction in early relapse leads to longer-term improvements in outcome. Unfortunately, most studies only provide medication treatment for 12–16 weeks. In the COMBINE trial, although the differences lost statistical significance, the beneficial effect of naltrexone persisted one year after discontinuation of treatment.⁵ For example, in that study, among patients receiving brief medical support and medication only, 55% had a good clinical outcome one year after treatment, compared to 43% of those taking placebo. Among subjects receiving up to 20 additional sessions of state-of-the-art behavior therapy, naltrexone patients still had better outcomes, although the difference was not statistically significant. Finally, those receiving behavioral therapy only, and no pills, did the worst of all, with only 47% having a good clinical outcome. In addition to providing evidence of the efficacy of naltrexone, this study also demonstrated the utter lack of any adverse effects on outcome of medication treatment. Furthermore, 17–36% of patients taking medications attended Alcoholics Anonymous meetings, strongly supporting the compatibility of these two modalities.⁵

Most pharmacotherapy studies have been highly controlled efficacy trials, raising questions about how the results will apply to "real world" patients. It is true that additional effectiveness trials are needed to represent "real-world" conditions in which exclusion criteria are minimized. However, effectiveness trials are expensive and lengthy. Most medical advances are implemented on the basis of efficacy trials and often with no high-level evidence of effectiveness. For example, the first

large effectiveness trials of treatments for depression, bipolar disorder, and schizophrenia were only recently completed, decades after widespread implementation of treatments based upon efficacy studies. Of course, individualizing care for a specific patient requires integrating the results and applying them in a given situation.

Medication development for alcohol treatment is relatively new, and more research is needed to identify novel compounds and better disease management strategies that will improve efficacy, especially over the long term. In the chronic form of alcohol dependence, one might have to treat patients much longer. Dissatisfaction with our current treatments is good if it motivates us to seek better ones, but it is destructive if it leads us to reject helpful treatments that are simply not as good as we want them to be. Behavioral treatment for alcohol dependence is only partially effective, and many patients fail to respond, or reject it altogether. It is likely that many patients would prefer pharmacotherapy over intensive behavioral treatment. To maximize the possibility of success, patients deserve access to all proven treatments, including medications.

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NEGATIVE REBUTTAL: DR. GITLOW

Picture ten alcoholic patients who happen to imbibe five drinks a day. Over the course of treatment, intake has decreased to three drinks a day. We have achieved something measurable.

We can draw graphs, plot curves, and sing victory songs, but unless we can demonstrate that this outcome has long-term value to the *alcoholic* patient, not simply to the heavy drinker, one thing we haven't demonstrated is alcoholism treatment efficacy.

A logical and successful treatment study for any disease requires that the disease be defined properly, that the experimental treatment be studied properly, and that we have achieved a well-characterized improvement in disease course. Dr. Willenbring refers to dozens of randomized controlled trials and the meta-analyses of those trials. But without proper inclusion criteria, comparison groups, or outcome measures, even hundreds of trials would not produce useful data.

Dr. Willenbring feels that the COMBINE study, an expensive multi-site trial supported by NIAAA (where Dr. Willenbring serves as a Division Director) and written by individuals, several with financial ties to a company producing a long-acting injectable formulation of naltrexone, confirmed naltrexone's efficacy. COMBINE had eligibility criteria that apply only to a minority subset of those with alcohol dependence, outcome measures that are unrelated to the disease definition, a failure to use a gold-standard treatment control, and a minimal treatment duration. If indeed it demonstrated efficacy, it failed to do so for anything that is clinically relevant for treatment of alcoholism—or alcohol dependence, for that matter.

The topiramate study to which Dr. Willenbring refers involved only a heavy drinking subset of subjects with alcohol dependence, was placebo-controlled but not compared with gold-standard treatment, ran only 12 weeks, and investigated only variations of self-reported alcohol intake quantities as outcome measures. Yes, topiramate did *something*; the study demonstrated that. But there was not a valid demonstration of the drug's efficacy in the treatment of alcohol dependence.

Dr. Willenbring says treatment for alcohol dependence is only partially effective. The Federal Aviation Administration has demonstrated an 85% rate of success in attaining recovery following diagnosis of alcoholism over a nine-year study period when pilots are followed closely by physicians.¹ In another study, continuous abstinence from alcohol was present in 77% of patients after two years of treatment using military protocols.² Neither program involved the use of medications. These findings are far more impressive than the comparatively unsuccessful results provided either with pharmacotherapy or by the inadequate control methods used to date in pharmacotherapy studies. Unfortunately, no studies of similar standard medical treatment, where the bulk of treatment is provided by physicians seeing patients weekly to monthly over many years, have been performed in a broad population. This is true despite the successful application of these methods within the private practice of addictive disease for over fifty years.

Why is it that when we already have an intervention that has produced long-term success in alcoholism treatment for decades, our governmental agencies are focused on the trivial

short-term reductions in alcohol intake that medications seem to produce among heavy drinking alcoholics? Is it the result of political pressure to reduce alcohol use in the population overall, pharmaceutical company pressure to open doors to an enormous potential market, confusion as to what is truly important in treatment of addictive disease, or a cost-reduction maneuver to add an adjunctive measure to the only partially effective treatment provided to alcoholics by non-physicians? Surely we're not going to buy in to findings based upon a series of misguided premises.

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AFFIRMATIVE REBUTTAL: DR. WILLENBRING

Demonstration that alcohol dependence is heritable does not imply that the “disease entity is present prior to the first drink.” What is inherited is a vulnerability to develop a disease, not the disease itself. Using Dr. Gitlow’s line of reasoning would lead to the absurd conclusion that because risk for coronary artery disease is heritable, coronary artery disease is present from birth despite the absence of plaque formation or myocardial ischemia, which only serve as “markers” for the underlying disease.

Dr. Gitlow also refers to “alcoholism,” which he distinguishes from DSM-IV alcohol dependence, although the basis for this distinction is not described. Dr. Gitlow’s “alcoholism” bears no relationship to alcohol consumption, and he asserts that a minority of people with “alcoholism” drink heavily. He incorrectly implies that the absence of formal integration of quantity and frequency of drinking into the DSM-IV criteria is equivalent to stating that intake bears no relationship to the disorder. In fact, there are frequent references to intoxication, tolerance, and withdrawal throughout the section on substance dependence in DSM-IV. It is true that one can be a heavy drinker in the absence of dependence,¹ but if the converse is true, it is unusual. Based on this idiosyncratic definition, he writes that no improvement has been demonstrated “in alcoholics,” that alcohol dependence is a subtype of sedative dependence, and that large numbers of alcohol-dependent subjects in clinical trials take other sedatives and are thus not

“in recovery.” Unfortunately, he offers no evidence to support any of these assertions.

Dr. Gitlow questions the treatment provided to control subjects in clinical trials. His gold standard is “treatment provided by physicians,” citing two descriptive studies of professional monitoring programs for pilots and physicians. Professionals who are monitored by regulatory agencies for long periods of time do have good outcomes, but that says nothing about whether treatment by physicians (as distinguished from the treatment *of* physicians) is superior to treatment by other professionals. Professionals typically receive extensive treatment in addition to that provided by physicians per se, not to mention long-term monitoring of body fluids for the presence alcohol and other substances. Dr. Gitlow’s gold standard is not applicable (or available) to most alcohol-dependent persons. In addition, many recent treatment studies provide state-of-the-art behavioral therapies to subjects in addition to medication.

Dr. Gitlow questions the relationship of quantity and frequency of drinking to morbidity and mortality in alcohol-dependent persons, but it is a strong relationship. For example, heavy drinking among dependent drinkers increases the odds of premature death by a factor of about 1.5.² The idea that large reductions in heavy drinking that are typical in non-abstinent individuals with alcohol dependence after treatment is unrelated to health defies logic.

Finally, he raises questions about the interpretation of outcome measures such as percent days abstinent. Admittedly, comparison of group averages of continuous outcome variables like percent days abstinent does not yield easily applicable results. However, that does not mean that they are without value. Various measures of drinking behavior are closely related to each other and to measures of function.³ Outcome measures continue to be refined, and the use of clinical significance methods and trajectory-based analyses can be expected to yield more clinically meaningful findings in studies of medications to treat alcohol dependence.

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