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Current Developments: Can *Campral* Cure Alcohol Abuse?[1]

ARTICLE

Mankind has been searching for a cure for alcoholism for eons. Yet the problems are still with us. Could there be a 'magic pill' that would work? The latest candidate, Campral (Acamprosate), now has the U. S. Government's approval. On July 30, 2004, CNN News reported, "The government approved the first new drug to treat alcohol abuse in a decade on Thursday, a medicine called Campral that promises to help ward off relapses." (FDA OKs 2004).

Campral, whose active ingredient is Acamprosate Calcium, was approved by the U. S. Food and Drug Administration on July 29, 2004, application number NDA 021431. It is an oral, delayed release tablet containing 333 mg. of the drug distributed in the U. S. by Lipha Pharmaceuticals. (Search FDA 2004).

Prior attempts to gain the FDA's approval had failed in previous years. The U. S. studies had included people still drinking rather than limit the participants to those who were abstaining. In these older studies, there was no statistical benefit with Campral over the placebo. Hence, the FDA denied approval. Conversely, Campral was being used successfully in other countries where the studies and usage were focused on participants who were no longer drinking. This was an important difference given the specific benefit this drug appears to have – that of helping an alcoholic stay abstinent. (How 2003). This is only the third drug to treat alcohol abuse to be approved for use in the United States. Naltrexone (ReVia) was approved almost ten years ago while it has been nearly fifty years since Disulfiram (Antabuse) was approved. (Bender 2002).

This writer was unable to obtain specifics about the development of the drug itself. Perhaps this is due to its development and use in Europe for many years prior to acceptance in the U. S. What is readily apparent is the need for treatments for alcoholism. Statistics vary, yet most state that between six and ten percent of the population is suffering some form of alcohol abuse or alcohol addiction. *Business Week's* article noted that fewer than five percent of the nation's alcoholics are being treated with drugs. (A Drug 2004). The article further noted that the vast majority of the approximately fourteen million alcoholics use therapy and support groups to help themselves. Admittedly, far too many receive no help at all. As we shall see later, these three approved drugs act in different ways and are useful at different stages of the quit/recovery process.

Campral has been approved and used in France and other European countries since 1989 where it is used mainly to prevent relapses. (Elchisak 2001). A French study completed in 1995 compared patients on two different doses of Campral and a placebo. The greatest success was with the group receiving the higher dosage, followed by the lower dose group. Still less success was noted with the placebo group. The group receiving the higher dose

experienced the greatest number of days of abstinence and clinical attendance. (Acamprosate 1996). While estimates vary as to Campral's use outside the U. S., The F. D. A. noted Campral is approved and available in twenty-eight countries. (FDA Approves 2004)

Australian researchers in 2001 noted using Naltrexone for heroin treatment finding it was less expensive and more effective than conventional treatments. They were using Naltrexone for both abstinence support and rapid detoxification. As noted, Naltrexone is approved in the U. S. for alcohol treatment as well. Perhaps many of these drugs will be found to help with more than one addictive drug. (Bender 2002).

Campral is identified by scientists as calcium acetylhomotaurine, better known as Acamprosate Calcium or Acamprosate. (Francesconi 1998). Campral helps keep people off alcohol once they have quit. Macnair (2004) noting it helps prevent relapse, called it an "…anti-craving drug…" It is not a drug for withdrawal or detoxification treatment. Neither does it appear to affect behavioral attitudes or a person's conditioning to alcohol. Current thinking is that Campral brings a "…hyperactive glutamate system back to normal levels…" which seems to dull withdrawal symptoms. (A Drug 2004). It is believed the glutamate system, when overactive, contributes to the exacerbation of withdrawal symptoms.

A recent work by scientists at The Scripps Research Institute found both alcohol and CRF, a brain peptide corticotrophin releasing factor, influence activity in the amygdala, the 'pleasure center' of the brain. Both increase the transmission of GABA, a neurotransmitter called gamma amino butyric acid. "There is a strong relationship between drugs of abuse, stress and the amygdala," says Neuropharmacology Professor George Siggins, who led the research. (Scientists 2004). Drugs that block CRF receptors are being studied as a possible treatment for other conditions which involve the CRF, such as panic disorders, depression and post traumatic stress disorder.

Campral is thought to work by modifying the action of GABA; thus it is called a synthetic GABA analogue. (Macnair 2004). This is based on structural similarities and in vitro data, noting that Campral does not share most of the other effects of GABA receptor modifying drugs." (Elchisak 2001). It is believed Acamprosate (Campral) decreases the effects of glutamate in the body. Since chronic alcoholism disrupts the glutamate system with changes lasting many months after ceasing drinking, it is possible that Acamprosate restores the glutamate system toward normal. Campral appears to decrease the 'high' of drinking and thus decreases the frequency of relapse during abstinence since the desired effect doesn't happen as expected. Additionally, Acamprosate appears to be able to prevent relapses rather than just reduce the effects of relapse. One researcher, Litten, found patients waited longer to take the first drink (relapse), had higher abstinence rates and competed treatment more often when taking Acamprosate than the placebo in his study. (Bender 2002).

As little as six years ago researchers attributed Acamprosate's efficacy in helping prevent relapse to its interactions with both the glutameatergic and GABAergic systems of the NAcc, an area of the brain thought to influence alcohol's reinforcement. (Francesconi 1998). Currently an article, appearing in the March 5, 2004 issue of the journal Science, by Siggins, et al, discusses studies of the cellular level changes with the use of alcohol through the GABA receptor function. "When neurons are exposed to alcohol," says Siggins, "they release CRF, and this causes the release of GABA in the amygdala. And when the CRF receptor is removed altogether (by genetic knock out), the effect of alcohol and CRF on GABA neurotransmission is lost." Possibly there is an underlying cellular mechanism involvement of CRF in alcohol's behavioral and motivational effects suggesting possible treatment via use of CRF antagonists. One study at Scripps found when the CRF antagonist was administered, alcohol no longer had an effect. "The response was totally gone-alcohol no longer did anything," noted Siggins. (Scientists 2004). Further research will be required because in the final analysis, exactly how Campral works is not known at this time.

As with any drug, there are side effects and cautions regarding its use. It is not a magic cure; it won't make someone quit drinking. It can help the patient to stay sober after having quit. Common side effects of Campral include an upset stomach, diarrhea, flatulence, nausea and headaches. Interesting to this writer is that these reactions sound very much like a hangover from too much alcohol. Less common side effects are skin reactions and altered libido, vomiting and itching. People who should not use Campral include pregnant and nursing women and anyone with severe kidney and/or severe liver problems. (Elchisak 2001 & Macnair 2004). Campral's interaction with other drugs has not been studied well to date. It does not appear to interact with other drugs used to treat alcoholism (Disulfiram and Naltrexone) or with antidepressant, anti-anxiety or sleep inducing medications. Further study is needed to learn more regarding this issue.

Results of trials regarding Campral's effectiveness have been promising. Those in Europe showed fifty percent of those on Campral abstained for three months while thirty nine percent of those on a placebo abstained for the same time period. After six months, those abstaining fell to thirty-five percent and then to thirty three percent a year later while on Campral. The comparable results of those on a placebo were twenty-three and twenty-one percent. (Macnair 2004). The initial results are more notable than the long term ones. One study done in 2003 compared people receiving Acamprosate alone, Naltrexone alone, the two combined, and a placebo. Both Acamprosate and Naltrexone were "…significantly more effective than placebo." (Miller 2003). Each individual drug and in combination were more effective in reducing relapse occurrences than the placebo. The combination of drugs was more effective in improving the length of time to the first drink than Acamprosate alone. The author concluded the combination can enhance effectiveness while not increasing adverse drug reactions. Another study in the U. S. led by Barbara Mason of Scripps Research Institute found patients using Campral along with behavioral therapy were abstinent only ten to fifteen percent longer than those taking a placebo and receiving therapy. Findings also showed no serious adverse effects or deaths in the six month, six hundred person study. This study was submitted for journal publication in August 2004. (A Drug 2004). The same Business Week article noted that Jennifer Potter, a research psychologist at Harvard Medical School, found all but two of the European trials showed Campral more effective than comparison treatment or placebo. One recent Brazilian study showed those receiving Acamprosate had lower relapse rates than the placebo group and the drug was well tolerated. (Baltieri 2004). The NIAAA's COMBINE Study is evaluating behavioral treatment alone and in combination with medications. This study is planned for a two year period using Naltrexone and Acamprosate. Hopefully results from this study will shed more light on which treatment modality will likely offer the best results. (NIAAA 2001).

Campral is generally recommended for patients who are able to abstain from all alcohol and other drugs. The President and CEO of Forest, the U. S. distributor stated, "The drug is meant for patients who are in some kind of program of psychosocial counseling." (A Drug 2004). The person must want to stop drinking. The ideal patient is one who is willing and able to take the medication, believes it can help and will cooperate with the treatment regime. Any drug can only do so much. The alcoholic and the drug must work together. The ideal patient is receiving treatment early enough to not yet suffer from the most damaging effects of alcohol consumption. A patient with severe liver, kidney or brain damage will probably not be able to cooperate sufficiently to benefit from Campral or, for that matter, any treatment.

The idea treatment environment using Campral appears to be when combined with social and psychological treatments or therapy. (Carpenter 2001) Abstinence rates increase when Campral is combined with psychosocial support as compared to using the drug alone. Patients with a strong support system of family, friends and employment are more likely to remain abstinent and be motivated to succeed. DiClemente (1999) noted that while most

treatment programs are action oriented, the patient may not be ready to take action. He believed patients go through a process internally before they are ready to change. Thinking, pondering and considering all come before the patient is ready to actually take action. Failure is to be expected when the patient is not ready, willing and able to cooperate with the treatment program. This seems obvious when explained. However, our society expects instant action and instant results leaving little room for a person to prepare themselves for the major changes abstinence requires.

A serious concern is the challenge of getting the new treatments to the addicts. Our health and social policies coupled with financial priorities seem to work to keep addicts from receiving treatment. Blaming the alcoholic is still a prevalent attitude. Our treatment facilities are vastly over worked and under funded often with a set of procedures in place which must be followed. Procedural flexibility would be ideal for the client but is not feasible given the current constraints. Addicts themselves present multiple barriers to treatment including refusal to participate, failure to follow instructions, unwillingness to suffer the side effects of therapeutic drugs, and perhaps the most challenging of all, that of refusing to believe there is a need for treatment. In the article, *Placement Matching: Challenges and Technical Progress*, Gastfriend (2000) summarized thusly, "To solve many of these problems, it will be necessary in the future to move from a model in which levels of care are predetermined and patient's needs are clustered to fit these criteria, to a patient-based model in which patient assessment is the starting point for determining the optimal service to provide."

As noted earlier, Antabuse and ReVia were approved for alcohol treatment prior to Campral's inclusion. Each is believed to work in different ways and be advantageous at different stages of an alcoholic's process to stop drinking. Antabuse (Disulfiram) reacts with alcohol to make the drinker very ill. If used, it is usually given in the initial detoxification stage of the process where its aversion effects are most noticeable. Antabuse blocks the breakdown of acetaldehyde in the liver thus leaving higher levels of alcohol in the body. Because the symptoms of this effect can be life threatening, Antabuse is not used as often now as it was in prior years. (Lawson 1988).

Naltrexone (ReVia) has principally been used in the treatment of opiate addiction with more recent use for alcoholism treatment. Naltrexone's mechanism is the blunting of the 'reward' circuit, blocking the brain chemicals which make a person feel good after drinking by hindering the elevation of dopamine. It has been used during detoxification and while trying to maintain abstinence. Naltrexone is more practical for the long term use since it has fewer side effects than Antabuse. (Bender 2002). Campral has been found to be effective only for those who have stopped drinking. Therefore, its optimal use is after the detoxification process has been successfully completed. Acamprosate is thought to stabilize the brain's glutamate system to make it feel normal thus making it effective in inhibiting alcohol consumption since the patient doesn't feel the strong need to drink. (FDA Approves 2004)

When the F. D. A. announced the approval of Campral it was noted that there are no therapeutic equivalents available. Perhaps that will change in the future as studies continue looking for effective treatments for alcoholism. One medication possibly useful for alcohol treatment is Topirimate, an anti-convulsant medication which has been shown to make withdrawal easier by reducing dopamine levels. Perhaps this can work where Disulfiram isn't effective or advised. (FDA Approves 2004). NIAAA is currently studying the efficacy of combining Naltrexone and Acamprosate. Other possible drugs under NIAAA research include Nalmefene (Revex), an opioid antagonist and Ondansetron, a serotonin antagonist. (Bender 2002). Scripps Research Institute has recently established the Pearson Center for Alcoholism and Addiction Research which hopefully will be on the cutting edge of research and able to rapidly bring new compounds to clinical trials. A plethora of new information is scheduled to be discussed at the International Society for Biomedical Research on Alcoholism, 12th World

Congress on Biomedical Alcohol Research to be held September 29th through October 2nd, 2004 in Heidelberg/Mannheim, Germany. (Preliminary 2004). Hopefully new information and useful treatments will be the result of this convening of some of the world's best thinking on the subject.

Conclusion

Can Campral cure alcohol abuse? In a word, No. Nothing can, in and of itself, cure alcohol abuse. If to cure is to be able to cease drinking, stay abstinent and live successfully, the cure requires a combined effort of whatever factors work for an individual to allow him/her to accomplish this goal. These factors include social support like Alcoholics Anonymous meetings, family and friends support, medication or a combination of medications, individual and/or group therapy, detoxification facilities, and treatment facilities to name a few. One or more kinds of assistance coupled with the individual's desire, willingness and ability to participate are required for success.

REFERENCES AND ADDITIONAL RESOURCES

A Drug to Recork Alcoholism's Demons. (2004). *Business Week/online/KTVU.com*. Aug. 2004. Retrieved 8/27/04 http://www.KTVU.com/money/3643230/detail.html

Acamprosate Offers Hope in Maintaining Abstinence. (1996). *Addiction Letter.* Jan. 96, Vol. 12, Issue 1. Retrieved 9/8/04 from EBSCO Host http://web12.epnet.com

Baltieri, D. A. & de Andrade, A. G. (2004). Acamprosate in Alcohol Dependence: A Randomized Controlled Efficacy Study in a Standard Clinical Setting. *Journal of Studies on Alcoholism,* Jan. 2004, Vol. 65, Issue 1, p. 136, 4 p. Retrieved 9/8/04 from EBSCO http://web12.epnet.com/citation.asp

Bender, K. J., Pharm. D., M.A. (2002). Addiction Treatment Progress and Obstacles. *Psychiatric Times*, May 2002, Vol. XIX, Issue 5. Retrieved 8/27/04 http://www.psychiatrictimes.com/

Carpenter, Siri. (2001). Mixing Medication and Psychosocial Therapy for Alcoholism. *Monitor on Psychology,* Vol. 32, No. %, June, 2001. Retrieved 8/27/2004 http://www.apa.org/monitor/jun01/mixingmed.html

DiClemente, C.C. (1999). Motivation for Change: Implications for Substance Abuse Treatment. *Psychological Science.* 10:209-213. Retrieved 9/2/04 http://www.psychiatrictimes.com

Elchisak, M.A., Ph.D. (2001). Acamprosate (Campral): Medication for Alcohol Abuse and Alcoholism Treatment. Retrieved 8/27/04 from http://www.doctordeluca.com/documents/acamprosatesummary.htm

F. D. A. Approves Acamprosate for Treatment of Alcohol Dependence. (2004). *Alcoholism & Drug Abuse Weekly*, Vol. 16, No. 30. Retrieved 9/8/04 from EBSCO http://web12.epnet.com/citation

F. D. A. OKs New Alcoholism Drug. (2004). CNN News (2004, July 30). Retrieved 8/27/04 http://www.CNN.com/2004/Health/07/30/sober.pill/ap/

Francesconi, B. F., WG. (1998). Acamprosate Enhances N-methyl-D-apartate receptor-mediated Neurotransmission but Inhibits Presynaptic GABA (B) Receptors in Nucleus Accumbens Neurons. *Alcohol Clin Exp Res.* 1998 Feb; 22(1); 183.91. Retrieved 8/27/04 http://www.biopsychiatry.com/acamprosate.htm

Gastfriend, D. R., Lu, S. H., Sharon, E. (2000). Placement matching: Challenges and Technical Progress. *Substance Use Misuse.* 35 (12-14): 2191-2213. Retrieved 9/2/04 http://www.psychiatrictimes.com

How's Euro-Health? (2003). *Men's Health*. Jan/Feb 2003, Vol. 18, Issue 1. Retrieved 9/8/04 from EBSCO Host http://web12/epnet/com

Lawson, G. W., Cooperrider, C. A. (1988). *Clinical Psychopharmacology.* Rockville, MD: Aspen Publishers, Inc.

Macnair, T. M.D. (2004). *Ask the Doctor*. BBC News (2004, August 27). Retrieved 8/27/04 http://bbc.co.uk/health/ask-doctor/alcohol-campral-drug.shtml

Miller, K. E. (2003). Dual Therapy for Prevention of Alcoholism. *American Family Physician*. 6/15/2003, Vol. 67, Issue 12, p. 2592, 2 p. Retrieved 9/8/04 from EBSCO Host http://web12.epnet.com

NIAAA's COMBINE Study. (2001). *Addiction Exchange.* Volume 3, No. 7, May 1, 2001. Retrieved 8/27/04. http://www.mid-attc.org/addex

Preliminary Program for International Society for Biomedical Research on Alcoholism – 12th World Congress. Heidelberg/Mannheim. (2004). Retrieved 8/27/04 http://www.isbra2004.de

Scientists at Scripps Research Institute Describe Dangerous Cocktail of Alcohol, Brain Peptides, and Neurotransmitters. (2004). *The Scripps Research Institute-News & Publications.* March 4, 2004. Retrieved 8/27/04 http://www.scripps.edu/news/press/030404.html

Search results for Application No. 021431. F. D. A. (2004). Retrieved 8/27/04 from http://www.accessdata.fda.gov/scripps/cder/drugsatfda/index.cfm

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