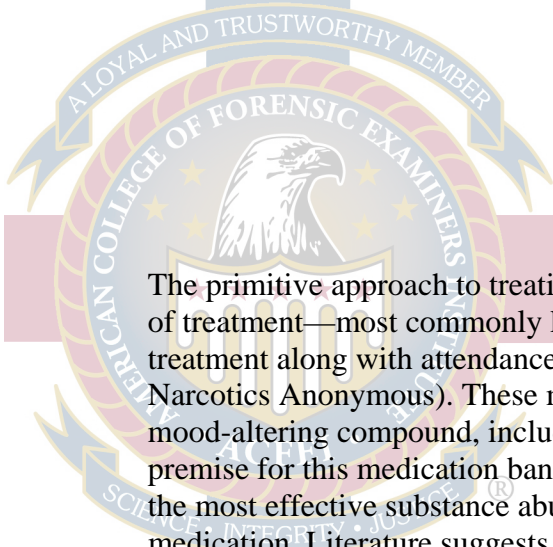




**Psychopharmacologic Treatment for Substance Abuse & Dependency:  
What the Literature Has to Say (A Meta-Analysis)**

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### **Abstract**

The primitive approach to treating substance abuse has been to follow the *disease model* of treatment—most commonly known as Alcoholics Anonymous—that involved group treatment along with attendance at support groups (e.g., Alcoholics Anonymous, Narcotics Anonymous). These models preached and demanded abstinence from any mood-altering compound, including prescribed medication. Although the original premise for this medication ban is understandable, modern research has demonstrated that the most effective substance abuse treatment intervention includes the use of anti-craving medication. Literature suggests that the use of anti-craving medications in conjunction with cognitive-behavioral intervention significantly increases abstinent rates. For those who returned to alcohol use after or while involved in these interventions, they consumed less quantities of alcohol and drank less frequently.

**Key Words:** substance abuse, Naltrexone (Revia), Acamprosate (Campral), anti-craving medications

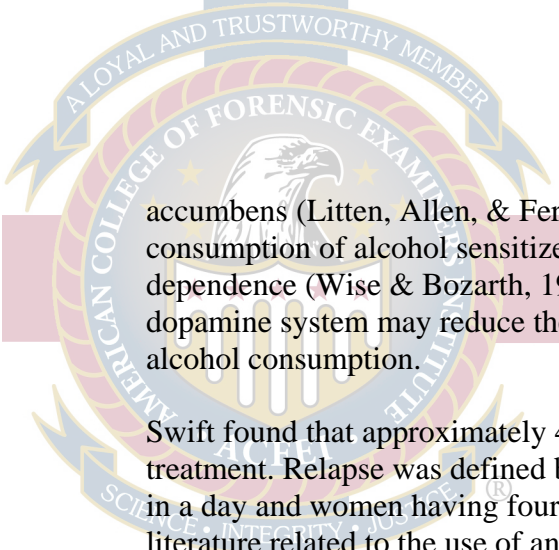
### **Introduction**

Will primarily focus on psychopharmacologic interventions for alcohol abuse and dependence. The implications for other types of substance abuse and dependence will be addressed in a more summative fashion and will address Nicotine, Marijuana, and Cocaine abuse/dependence; Suboxone is not addressed and should be further explored. Although not an exhaustive review, the following information helps bring to light the importance of psychopharmacologic intervention in the effective treatment of substance abuse and substance dependence.

One reason why the treatment of substance abuse needs to be addressed again is that a significant number of individuals experience some degree of impairment as a result of substance use and abuse. In addition, the courts are consistently addressing the degree to which criminals are to be held accountable for their actions if they were impaired in any way by substances. Effective treatment interventions continue to be explored and need to be reviewed periodically, which is one reason for this review. In the past, many substance abuse treatments focused on the belief that individuals were “powerless” over the substance and that treatment should avoid the use of medications. The current research and literature suggests that medication and supportive intervention appear to produce the most effective substance abuse intervention.

### **Anti-craving Medication & Effective Substance Abuse Intervention**

Treating substance abuse with anti-craving medication has been found to be effective. Anti-craving medications help lessen the struggle to achieve abstinence and research continues to support this premise as indicated below. Alcohol affects several brain neurotransmitters (e.g., dopamine, gamma-amino butyric acid, glutamate, serotonin, adenosine, norepinephrine, and Opioid peptides and their receptors), and several neurobehavioral effects of alcohol have been related to the development of alcohol dependence (Swift, 1999). The pleasurable and stimulant effects of alcohol are mediated by a dopaminergic pathway projecting from the ventral tegmental area to the nucleus



accumbens (Litten, Allen, & Fertig, 1996; Chick & Erickson, 1996). Repeated excessive consumption of alcohol sensitizes this pathway and leads to the development of dependence (Wise & Bozarth, 1987; Robinson & Berridge, 1993). Drugs that target this dopamine system may reduce the reinforcing effects of alcohol and thereby reduce alcohol consumption.

Swift found that approximately 40-70% of patients resume drinking within one year of treatment. Relapse was defined by Volpicelli (2005) as a man having five or more drinks in a day and women having four or more drinks in a day. The following is a review of the literature related to the use of anti-craving medications.

### **Disulfiram (Antabuse)**

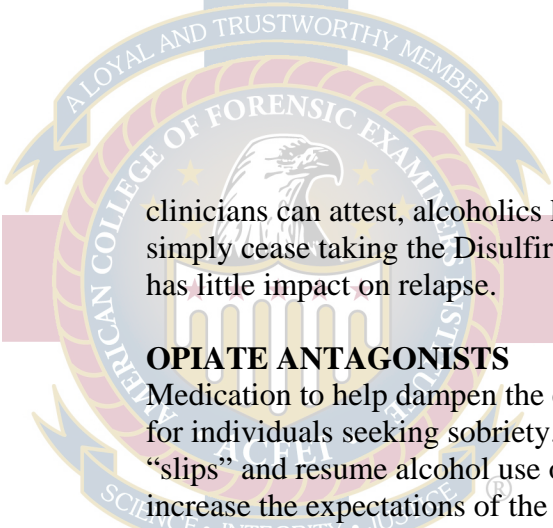
Overall the use of Disulfiram (Antabuse) has not proven overly effective to help individuals achieve sobriety. Disulfiram has been available for over 50 years and is used as a deterrent to alcohol use. Disulfiram interferes with the positive effects of alcohol ingestion. When alcohol is consumed, the Disulfiram causes unpleasant symptoms, including flushing, palpitations, difficulty breathing, headache, and nausea (Swift, 1999; 1999b; Brewer, 1995).

Fuller, Branchey, & Brightwell et al. (1986) found that compliance turned out to be the most important predictor of remaining abstinent. Patients who were compliant in taking Disulfiram had a much higher abstinence rate than patients who were noncompliant. However, there was no improvement in abstinence rates for patients that took Disulfiram compared to those that took placebo. This suggests that compliance with treatment recommendations and a will to remain abstinent may play a more significant role in maintaining abstinence than taking Disulfiram.

Krampe et al. (2006) found that even after ceasing the use of Disulfiram, over 50% of the subjects in this study remained abstinent after a nine year follow-up period. This success was attributed primarily to the psychological effect of having taken the medication and perhaps the increased sense of self-efficacy to remain abstinent even after cessation of the medication (generally having taken Disulfiram for at least two years). Supervised intake of the medication improved the outcome.

Use of Disulfiram was found to decrease drinking days for those who resumed drinking. However, this effect may have resulted from chance (*e.g.*, Fuller et al., 1986; Kranzler et al., 2003).

Swift (1999b) found that Disulfiram does not significantly increase the success of alcohol treatment (Hughes & Cook, 1997). Several studies have found that Disulfiram neither improves the rate of continuous abstinence nor delays the resumption of drinking, but it may reduce drinking after relapse (Fuller, Branchey, Brightwell, et al., 1986; Peachey & Annis, 1989; Hughes & Cook, 1997). Use of the medication, however, may decrease the quantity and frequency of alcohol consumption by recovering alcoholics (Chick et al., 1992; Fuller et al., 1986), but the medication itself does not appear to increase the proportion of patients who maintain total abstinence (Hughes & Cook, 1997). As



clinicians can attest, alcoholics know that when they want to consume alcohol, they simply cease taking the Disulfiram; thus, coming to the conclusion that taking Disulfiram has little impact on relapse.

### **OPIATE ANTAGONISTS**

Medication to help dampen the effects of alcohol ingestion serve to increase success rates for individuals seeking sobriety. It has been expected that alcoholics will experience “slips” and resume alcohol use on occasion. This expectation, however, may also increase the expectations of the alcoholic to “slip”. Regardless of what the motivation for the “slip”, Opioid antagonists interfere with the absorption of alcohol and therefore the pleasant effects of alcohol are not experienced or at least not experienced to a significant degree, therefore aiding the individual’s efforts to achieve and maintain sobriety. Below is what the literature has to say.

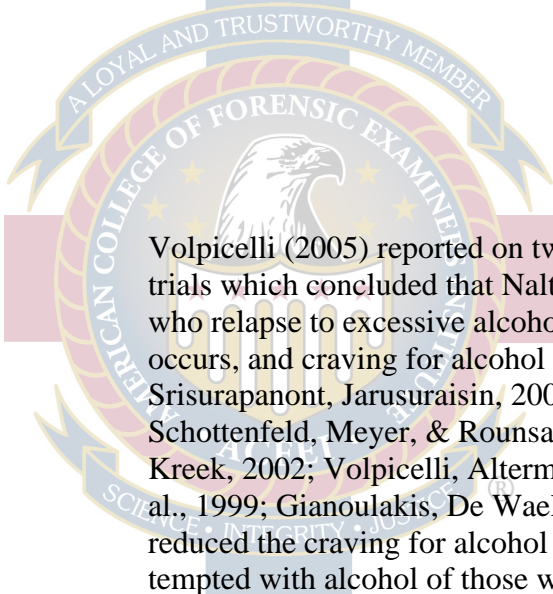
Johnson & Ait-Daoud (1999) indicate that Opioid peptides are a class of neurotransmitters that produce physiological effects similar to those produced by morphine and heroin and modulate the effects of other neurotransmitters, especially dopamine. Opioid peptides appear to increase the rewarding effects of alcohol, nicotine, and opiates, which serves to reinforce their repeated use. Herz (1997) indicates that the production, release and activity of Opioid peptides are affected by alcohol consumption. Medications that block Opioid activity may block the reinforcing effects of alcohol. Mu-Opioids (Morphine-like) are useful in the treatment of alcohol dependence. The Mu-Opioid antagonists block the alcohol induced release of dopamine in the nucleus accumbens (Gessa, Muntoni, Colu, Vargiu, & Mereu, 1985; Benjamin, Grant, & Pohorecky, 1993). Several of the Mu-Opioids are discussed below. Mu receptors have been implicated in some alcohol-related behaviors (Herz, 1997).

#### ***Naltrexone (ReVia, Trexan)***

Naltrexone has been shown to reduce drinking and increase abstinence by reducing the positive reinforcing, pleasurable effects of alcohol. For those taking Naltrexone, individuals relapsed approximately at a 19% to 40% lower rate (Kranzler et al., 2003 & 2006). Social drinkers report less positive and more sedative and unpleasant effects of alcohol when taking Naltrexone (Swift, Whelihan, Kuznetsov, Buongiorno, & Hsuing, 1994). Patients with alcoholism who drink during treatment with Naltrexone report experiencing less alcohol “high” and are less likely to progress to heavy drinking (Volpicelli, Alterman, Hayasgida, & O’Brien, 1992; Volpicelli, Watson, King, Sherman, & O’Brien, 1995). Naltrexone also reduces the craving for alcohol in both alcoholic patients (Monti, Rohsenow, Swift, Abrams, Colby, & Mueller, in press; Chick, Anton, Checinski, Croop, Drummond, Farmer, Labriola, Marshall, Moncrieff, Morgan, Peters, & Ritson, 2000; O’Malley et al., 1992; Volpicelli et al., 1992; Volpicelli et al., 1995; Volpicelli et al., 1997; Mason et al., 1994, 1999) and social drinkers (Davidson, Swift, & Fitz, 1996). O’Brien (2005) indicates that Naltrexone can also help with former Opioid addicts.

Patients that received medical management with Naltrexone, with or without cognitive-behavioral treatment interventions, demonstrated significantly more resistance to relapse (Anton et al., 2003).





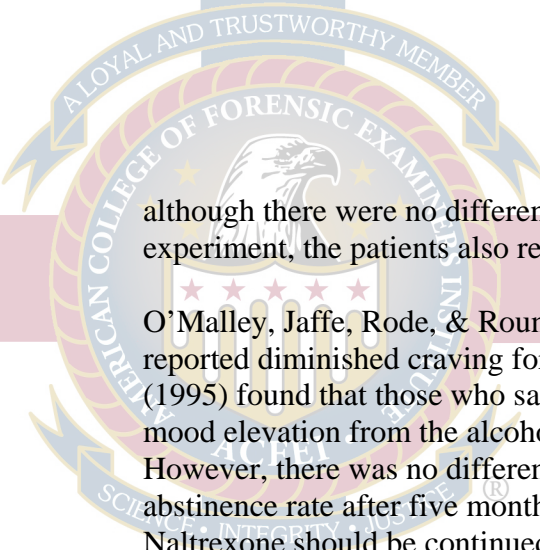
Volpicelli (2005) reported on two reviews of more than two dozen randomized clinical trials which concluded that Naltrexone significantly reduces the percentage of patients who relapse to excessive alcohol use, the percentage of days in which alcohol drinking occurs, and craving for alcohol (Garbutt, West, Carey, Lohr, & Crews, 1999; Srisurapanont, Jarusuraisin, 2005). Several studies (O'Malley, Jaffe, Chang, Schottenfeld, Meyer, & Rounsaville, 1992; O'Malley, Krishnan-Sarin, Farren, Sinha, & Kreek, 2002; Volpicelli, Alterman, Hayashida, & O'Brien, 1992; Anton, Moak, Waid, et al., 1999; Gianoulakis, De Waele, & Thavundayil, 1996) reported that Naltrexone use reduced the craving for alcohol even in high-risk situations in which the patient was tempted with alcohol of those with family histories of alcoholism.

Volpicelli (2005) found that Naltrexone reduces alcohol drinking and particularly a relapse to excessive alcohol drinking. He pointed out that Naltrexone does not prevent patients from having a "slip", but it did help prevent one drink from turning into a relapse (Volpicelli, Watson, King, Sherman, & O'Brien, 1995; Volpicelli et al., 1992). In his study, Volpicelli (1995) found that Naltrexone was associated with a reduction of approximately 50% in relapse rates. Another study reported that Naltrexone was associated with a 38% reduction in alcohol relapse (Srisurapanont, Jarusuraisin, 2005). King, Volpicelli, Frazer, & O'Brien (1997) found that nonalcoholic social drinkers (average consumption of two drinks per day), even, experienced less of the alcohol's stimulant effects when they took Naltrexone hours before drinking.

Volpicelli, Alterman, Hayasgida, & O'Brien (1992) found that recently abstinent male patients who were receiving psychosocial alcoholism treatment and receiving 50mg per day of Naltrexone for 12 weeks reported fewer cravings than subjects who received the psychosocial treatment alone. In addition, they found that those taking the Naltrexone maintained abstinence for longer periods and exhibited significantly less relapse rates than those not taking Naltrexone (23% of Naltrexone treated patients compared to 54% of placebo treated patients experienced relapse). Even among patients who sampled alcohol while in treatment, only 50% of the Naltrexone treated patients relapsed, compared with 95% of the patients receiving the placebo. Additionally, fewer later resumed heavy drinking (consuming five or more drinks in a day). O'Malley et al. (1992) reported that less than half of the patients in the Naltrexone group resumed heavy drinking as compared to more than 80% of the patients in the placebo or untreated group. Naltrexone was most effective for those patients who reported strong cravings at the beginning of the study (Jaffe, 1996).

Naltrexone was found to reduce cravings and recently abstinent patients were less likely to report cue-induced craving than patients receiving placebo. Of those who reported craving, the absolute intensity of the craving had not decrease from levels measured at the start of the experiment (Monti et al., 1999; Swift, 1999b).

Davidson et al. (1996, 1999) found that when on Naltrexone versus the placebo, there were significant increases in latency to sip between the first and second alcoholic drinks,



although there were no differences in self-reported urges to drink. During the second experiment, the patients also reported less of an urge to drink when on Naltrexone.

O'Malley, Jaffe, Rode, & Rounsaville (1996) found that alcoholics using Naltrexone reported diminished craving for alcohol. Volpicelli, Watson, King, Sherman, & O'Brien (1995) found that those who sample alcohol after a period of abstinence experience less mood elevation from the alcoholic beverage than non-Naltrexone treated patients. However, there was no difference between the placebo and Naltrexone groups in abstinence rate after five months after going without the Naltrexone, suggesting that the Naltrexone should be continued to support long-term abstinence.

One notable limitation is that Naltrexone has not been found to be effective with chronic, severe alcoholic veterans (Krystal, Cramer, Krol, Kirk, et al., 2001). There was no difference between those patients who used Naltrexone or placebo in preventing or delaying relapse to heavy drinking, reducing the number of drinking days, or decreasing the amount of alcohol consumed during episodes of drinking. In addition, for this population, the authors found no significant positive influence of participation in psychosocial treatment or Alcoholics Anonymous meetings. The authors found that good compliance with prescribed medication, attending more counseling sessions, and participation in Alcoholics Anonymous resulted in more positive outcomes, and with those patients prescribed Disulfiam, Lithium, or placebo groups; again, Naltrexone did not produce positive effects in this population of severe, chronic alcoholic veterans (Krystal et al., 2001; Collins & Dorus, 1991; Fawcett, Clark, Aagasen, et al., 1987).

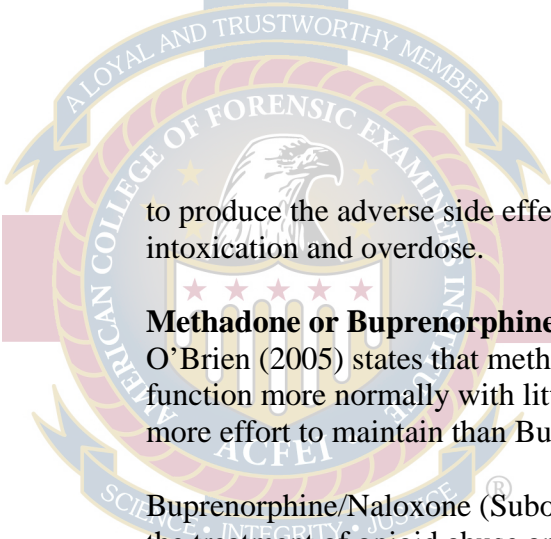
Chick et al. (2000) indicated that compliant patients experienced a reduction of alcohol intake, which appears to support the hypothesis that Naltrexone reduces loss of control which some dependent drinkers experience when they start to drink (Volpicelli et al., 1995b) or that Naltrexone reduces the amount of alcohol consumed by reducing the euphoric effect or inducing an adverse effect of drinking alcohol (e.g., Swift et al., 1994; Davidson et al., 1999). However, abstinence was only achieved by approximately 20% of the patients involved in Chick et al.'s (2000) study thereby suggesting that Naltrexone does not help achieve abstinence but rather reduces the cravings. Patients who took Naltrexone drank less heavily.

#### Obstacles of Using Naltrexone

The primary obstacle to the effectiveness of Naltrexone is poor patient compliance. Volpicelli et al. (1997) and Litten & Allen (1998) found that those who maintained their abstinence were those who complied with their daily dose of Naltrexone at least 80-90% of the time.

Advantages of Naltrexone include that it cannot be abused, does not produce dependency, and has few minor side effects (Rawson, McCann, Hasson, & Ling, 2000), and that it can be administered with other medications such as Acamprosate and antidepressants (e.g., Kranzler et al., 2006).

**Nalmefene** (*Revex*) is a Mu receptor that has been demonstrated to increase abstinence (Mason, Rezvani, Grady, & Garbutt, 1994). Nalmefene is also less likely than Naltrexone



to produce the adverse side effect of liver damage. This drug is also used for Opioid intoxication and overdose.

### **Methadone or Buprenorphine**

O'Brien (2005) states that methadone and Buprenorphine enables former addicts to function more normally with little or no drug craving. Methadone appears to require more effort to maintain than Buprenorphine.

Buprenorphine/Naloxone (Suboxone) is an opioid antagonist that has proven effective in the treatment of opioid abuse and dependence (Ormon & Keating, 2009). It blocks or reverses the effects of Opioids. It has proven equally effective as methadone but with advantages such as a decreased risk for overdose. Suboxone creates a negative reaction in the user when they use opioids.

## **SPECIFIC GLUTAMATE ANTAGONISTS**

Addressing the physiological cravings with medication lessens the strength of cravings which in turn would serve to make sobriety more desirable and more easily attained for the alcoholic. Below is what the research has to say.

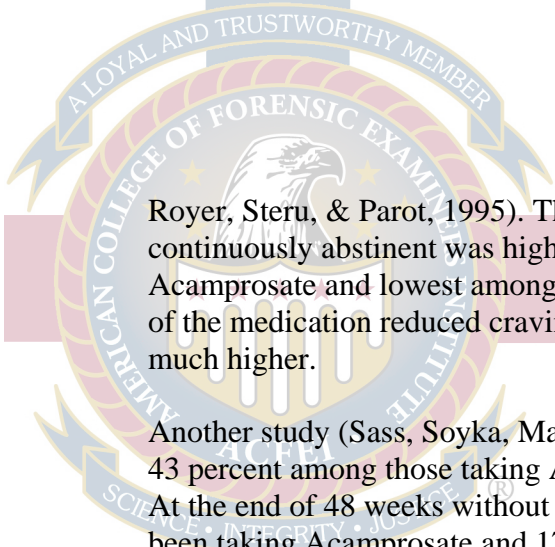
The NMDA-receptor antagonist Acamprosate has been found to reduce the intensity of the cravings after drinking cessation, even when the patient is exposed to situations or environments associated with previous alcohol use, where the risk for relapse would appear to be the greatest (Spanagel & Zieglansberger, 1997).

### ***Acamprosate (Campral)***

Has been shown to decrease the intensity of craving after a person has stopped drinking. Acamprosate interacts with the GABA neurotransmitter system and inhibits the excitatory NMDA receptor. Acamprosate reduces the hyperactivity in the NMDA system during alcohol withdrawal, especially for patients with protracted withdrawal symptoms (Volpicelli, 2005). Rawson et al. (2000) found that one of the factors in relapse is negative mood states and that Acamprosate reduces the severity of the negative mood states and relapse triggers and therefore contributes to achievement and maintenance of abstinence in the early weeks and months of recovery.

Swift (1999; 1999b) found that patients who took Acamprosate in conjunction to treatment were twice as likely to remain abstinent from alcohol for up to one year following treatment when compared to patients who received only a placebo. Lhuintre, Moore, Tran, Steru, Langrenon, Daoust, Parot, Ladure, Libert, & Boismare (1990) found similar results, in addition to which they found that the greatest improvement was found in the most severe alcoholics. Litten et al. (1996) found that Acamprosate increased the number of patients who remained abstinent as well as the duration of abstinence; however, it did not have a consistent impact on craving for alcohol.

One study found that patients taking 2.0 grams per day and 1.3 grams of Acamprosate per day to be far superior to a placebo in the treatment of alcohol-dependent patients who drank an average of approximately 17 standard drinks per day (Paille, Guelfi, Perkins,



Royer, Steru, & Parot, 1995). They found that the highest percentage of patients continuously abstinent was highest among those taking two grams per day of Acamprosate and lowest among those taking a placebo. They also found that higher doses of the medication reduced cravings at three months, when the intensity of craving was much higher.

Another study (Sass, Soyka, Mann, & Zieglgansberger (1996) found abstinence rates of 43 percent among those taking Acamprosate compared with 21% of those taking placebo. At the end of 48 weeks without medication, abstinence rates were 39% for those that had been taking Acamprosate and 17% for those on placebo. Other studies have found similar results (e.g., Whitworth, Fisher, Lesch, Nimmerrichhter, Oberbauer, Platz, Potgieter, & Fleischhaker, 1996; Geerlings, Ansoms, & Van Den Brink, 1997). 60% of the patients in another study receiving Acamprosate remained abstinent as compared to 22% of those receiving placebo (Lhuintrc, Moore, Tran, et al., 1990).

Acamprosate reduces the tendency to return to drinking alcohol after detoxification. It does not cause physical dependence and has no significant withdrawal symptoms. Volpicelli (2005) summarized that Naltrexone generally improves relapse rates and alcohol craving, but has little effect on total abstinence. Acamprosate, he indicated, produces significant improvement in abstinence rates and increases the time before any drinking occurs (Bouza, Angeles, Munoz, & Amate, 2004; Kranzler et al., 2006; Mason, 2001; Wilde & Wagstaff, 1997).

Mason (2003) and McGrath, Nunes, Stewart et al. (1996) both found patients with coexisting depression and alcohol abuse experienced improved treatment outcomes when using Acamprosate. The medication improved the depressive symptoms and also reduced the number of days of drinking.

Negative effects include poor patient compliance and that it is excreted by the kidney, so those with renal insufficiency should not take it. The positive benefits include that it is not impacted by liver problems and does not cause liver problems, there is no abuse potential, and there is no sedation effect.

## **SEROTONERGIC MEDICATIONS**

Addressing depressive symptoms also appears to increase success for attaining sobriety. Numerous studies have found that increasing levels of Serotonin helped significantly improve abstinence efforts. Perhaps because improving mood lessens the desire for alcohol and improving the alcoholic's overall self-esteem and ability to sleep and eat is a more healthy way to support sobriety.

Serotonin plays a role in regulating diverse physiological functions, including body rhythms, sleep, mood states, appetite, and consummatory behaviors (Lovinger, 1997). Alcohol consumption alters the Serotonin-receptor function by stimulating the Dopaminergic activity, which in turn produces the rewarding effects of the alcohol (Lovinger, 1997).





### **Selective Serotonin Reuptake Inhibitors (SSRI's)**

SSRI's are medications that interfere with the removal of Serotonin from the synapse following release of the neurotransmitters. Medications such as Fluoxetine, Sertraline, and Citalopram, which are used as antidepressants and anxiolytic drugs, increase serotonergic function and has been found to reduce alcohol consumption by 15-20% (Naranjo, Sellers, Sullivan, Woodley, Kadlec, & Skyora, 1987; Naranjo, Poulos, Bremner, & Lanctot, 1994). These patients report a decreased desire and liking for alcohol. However, the results with patients diagnosed with alcohol dependence have been less impressive, finding that alcohol intake decreased only during the first week of treatment, and no difference noted thereafter (Gorelick, 1993; Kranzler, Burleson, Korner, et al., 1995).

Use of SSRI's can reduce alcohol consumption in alcohol abusers (Naranjo, Kadlec, Sanhueza, Woodley-Remus, & Sellers, 1990; Naranjo, Poulos, Bremner, & Lanctot, 1992; Naranjo & Sellers, 1989). Naranjo et al. (1994) found that the use of SSRI's reduced overall alcohol consumption in heavy drinkers by approximately 15-20%. However, long-term studies have not replicated these findings (Gorelick & Paredes, 1992; Kranzler, Burleson, Korner, Boca, Bohn, Brown, & Liebowitz, 1995).

Several studies (Buydens-Branchey, Branchey, & Noumair, 1989; Fils-Aime, Eckardt, George, Brown, Mefford, & Linnoila, 1996) have found that alcoholics with an early onset of disease may be deficient in Serotonin (5HT). Although an SSRI such as Prozac (Fluoxetine) should compensate for this deficit in cases of early onset alcoholism, it was found that Prozac appeared to actually increase alcohol consumption among early onset alcoholics (Kranzler, Burleson, Brown, & Babor, 1996).

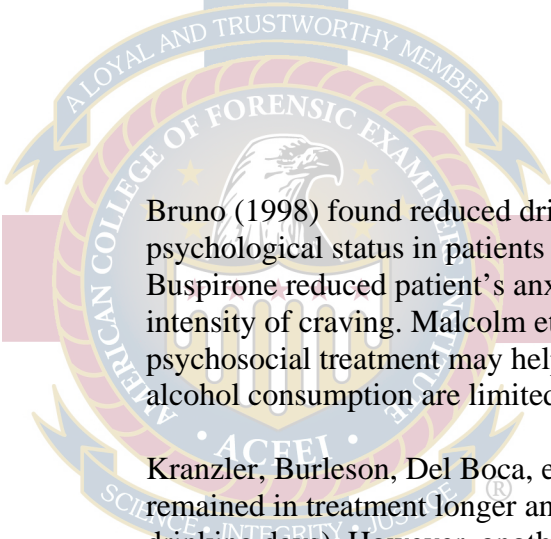
However, the use of SSRI's has been found to be effective for alcoholics who have coexisting depression. Cornelius, Salloum, Ehler, Jarrett, Cowmus, Perel, Thase, & Black, (1997) found that both depressive symptoms and the level of alcohol consumption decreased significantly in patients who were given Prozac compared with those who were given a placebo.

### **Specific Serotonin Receptor Subtypes**

Some subtypes of the Serotonin receptors may be involved in general consummatory behavior as well as the development of alcohol intoxication and alcoholism (Loving, 1997).

**Buspirone** (*Buspar*) is commonly prescribed to treat anxiety disorders. Johnson & Ait-Daoud (1999) comment that some studies suggest that alcoholics treated with Buspirone may exhibit some improvement in both craving and drinking behavior. Buspirone may work by reducing alcohol-related behaviors that may result in reductions in anxiety, rather than through a reduction in the rewarding effects of alcohol per se, and that any potential benefit from Buspirone is likely limited to alcoholics with independent coexisting anxiety disorders (Malec, Malec, & Dongier, 1996).





Bruno (1998) found reduced drinking, less craving, and improved social and psychological status in patients receiving Buspirone. Tollefson et al. (1992) found that Buspirone reduced patient's anxiety levels, number of days craving alcohol, and the intensity of craving. Malcolm et al. (1992) found that although Buspirone combined with psychosocial treatment may help ameliorate psychiatric symptoms, the drug's effects on alcohol consumption are limited.

Kranzler, Burleson, Del Boca, et al. (1994) found that anxious patients taking Buspirone remained in treatment longer and drank less than those receiving placebo (4 versus 10 drinking days). However, another study found no significant difference between Buspirone and placebo (Malcolm, Anton, Randall, Johnston, Brady, & Thevos, 1992).

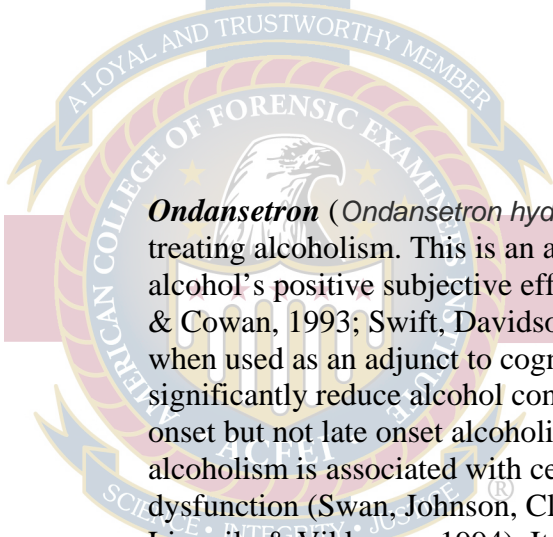
***Citalopram (Celexa)***

Kranzler et al., (1995) found that the use of Celexa reduced both drinking and self-reported craving for alcohol. However, for some alcoholics, these reductions appear to be transient.

***Fluoxetine (Prozac)***

Kabel & Petty (1996) found no differences in drinking outcomes among severe alcoholics (average of 19 or more drinks per day) who were treated with Fluoxetine or placebo.

***Ritanserin*** is another Serotonin Subtype receptor that may play a role in alcohol's rewarding effects as well as to the development of acute physical withdrawal symptoms (Loving, 1997). Studies suggest that patients who were prescribed 5mg per day of Ritanserin concurrent with cognitive-behavioral therapy had significantly reduced their alcohol consumption. However, other studies have found no difference in drinking level was observed between patients receiving Ritanserin and those taking the placebo (Litten et al., 1996; Johnson, Jasinski, Galloway, Kranzler, Weinreib, Anton, Mason, Bohn, Pettinati, Rawson, & Clyde, 1996).



**Ondansetron** (*Ondansetron hydrochloride and dextrose*) appears to be promising for treating alcoholism. This is an antiemetic medication. This drug reduces some of the alcohol's positive subjective effects, including the self-reported desire to drink (Johnson, & Cowan, 1993; Swift, Davidson, Whelihan, & Kuznet, 1996). They also found that when used as an adjunct to cognitive-behavioral treatment, Ondansetron was found to significantly reduce alcohol consumption and increased abstinence rates among early onset but not late onset alcoholics. It was found that an alcoholic with early onset for alcoholism is associated with certain biochemical measures believed to indicate Serotonin dysfunction (Swan, Johnson, Cloninger, & Chen, 1999; Buydens-Branchey et al., 1989; Linnoila & Vikkunen, 1994). It is believed that Ondansetron treatment effect may be associated with its ability to lessen serotonergic abnormality in this subtype of alcoholic. However, other compounds that facilitate Serotonin function to replace a Serotonin deficit may have no effect or may worsen drinking behavior of early onset alcoholics (Kranzler et al., 1994a, 1994b). Ondansetron moderately reduced alcohol consumption, although for the heaviest drinkers the treatment effect was less clear (Sellers et al., 1994). Additional medications have been found to improve abstinence rates for alcohol and other drugs. The following is a review of the literature; however, this is not an exhaustive review.

### **DOPAMINE ANTAGONISTS**

Dopamine antagonists can block the reinforcing effects of alcohol (Broadbent, Grahame, & Cunningham, 1995). Antagonists may alleviate a dopamine-deficiency state (George, Fan, Ng, Jung, O'Dowd, & Naranjo, 1995).

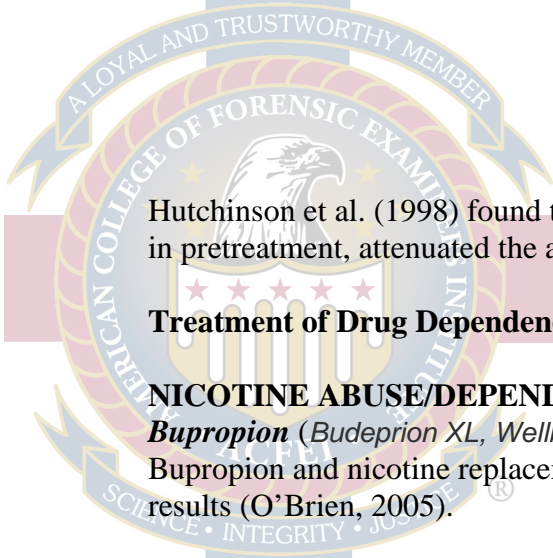
**Tiaprider** (*Tiaprider*) is an antipsychotic medication that has been demonstrated to adjust low-dose alcohol-induced hyperactivity and higher doses are associated with sedation (Johnson & Ait-Daoud, 1999). Shaw, Waller, Majumdar, Alberts, Latham, & Dunn (1994) found that Tiaprider was superior to a placebo in increasing abstinence, self-esteem, and life satisfaction, and further found that drinking levels also were significantly lower when using Tiaprider. Swift (1999) found that Tiaprider may be useful in alleviating alcohol-withdrawal symptoms and for acute and chronic alcoholism (Peters & Faulds, 1994). Those patients that were compliant with Tiaprider were more likely to remain abstinent and had lower rates of use of health care services (Shaw, Waller, Majumdar, Alberts, Latham, & Dunn, 1994).

An important problem identified with the use of Tiaprider is their potential to produce neurological side effects such as movement disorders (Tamion, Pent, Massair, Leroy, Biga, & Oksenhendler, 1990) and seizures (Delmeire, 1980). The side effects may limit the use of Tiaprider with some patients.

### **Haloperidol (Haldol)**

Patients using Haloperidol reported fewer cravings for alcohol and consumed less of their preferred alcoholic beverage (Modell et al., 1993). However, the literature is clear about the risks of long-term use of this medication, which may result in neurological damage.

### **Olanzapine (Zyprexa)**



Hutchinson et al. (1998) found that the anti-psychotic medication Olanzapine, when used in pretreatment, attenuated the alcohol-induced stimulation and cue-induced craving.

## **Treatment of Drug Dependence Other Than Alcohol**

### **NICOTINE ABUSE/DEPENDENCY**

**Bupropion** (*Budeprion XL, Wellbutrin*)

Bupropion and nicotine replacement are often used in a coordinated fashion with good results (O'Brien, 2005).

**Rimonabant** (*Acomplia, Bethin, Monaslim, Remonabant, Riobant, Slimona, Rimoslim, Zimulti, [Zimulti](#) and Riomont*)

O'Brien (2005) indicated that Rimonabant acts in a similar fashion to Naltrexone and is effective for addressing nicotine dependency.

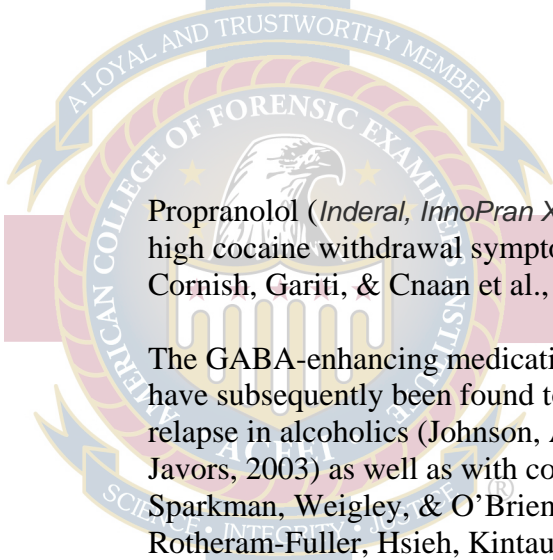
### **MARIJUANA ABUSE/DEPENDENCY**

O'Brien (2005) indicated that Rimonabant is effective for patients who abuse marijuana because it blocks the endogenous cannabinoids and therefore helps to block the positive effects of the marijuana. Under certain conditions, this medication can also reduce food intake, alcohol intake, and block reinstatement of cocaine and heroin self-administration (De Vries, Shaham, Homberg, Cromberg, Schurman, Dieben, Vanderschuren, & Schoffelmeer, 2001; Vickers, Webster, Wyatt, Dourish, & Kennett, 2003). However, Rimonabant continues to be experimental in nature.

Naltrexone was found to actually increase many of the positive subjective effects of oral THC in heavy marijuana smokers (Haney, Bisaga, & Foltin, 2002). At low doses, Naltrexone had few effects on low dose THC, and did not affect the subjective, physiological or behavioral effects of low THC doses (Wachtel & de Wit, 2000; Haney et al., 2002). In fact, Haney et al. (2002) found that Naltrexone enhanced the subjective effects of low dose THC use. Therefore it appears that the use of Naltrexone with THC users is contradicted.

### **COCAINE ABUSE/DEPENDENCY**

O'Brien (2005) indicates that there are medications already approved for addressing cocaine abuse. Disulfiram was found to help those who met criteria for cocaine abuse and dependency alone, with no significant accompanying alcohol problem (Carroll, Fenton, Ball, Nich, Frankforter, Shi, Rounsaville, 2004, & Vocci & Ling, 2005). Disulfiram and related medications have shown to reduce cocaine use in several clinical studies (*e.g.*, Vocci & Ling, 2005). However, no medications tested to date have demonstrated effective reduction to methamphetamine use. Modafinil was initially approved for the treatment of narcolepsy. Dackis & O'Brien (2003) and Dackis, Kampman, Lynch, Pettinati, & O'Brien (2005) found that use of Modafinil reduced the high from cocaine and reduced the cocaine craving.



Propranolol (*Inderal*, *InnoPran XL*) significantly reduced relapse in cocaine addicts with high cocaine withdrawal symptoms (Kampman, Volpicelli, Mulvaney, Alterman, Cornish, Gariti, & Cnaan et al., 2002).

The GABA-enhancing medications were originally used to treat seizure disorders and have subsequently been found to help with mood stabilization. Topiramate helped reduce relapse in alcoholics (Johnson, Ait-Daoud, Bowden, DiClemente, Roache, Lawson, & Javors, 2003) as well as with cocaine addicts (Kampman, Pettinati, Lynch, Dackis, Sparkman, Weigley, & O'Brien, 2004) and to reduce cocaine use (Shoptaw, Yang, Rotheram-Fuller, Hsieh, Kintaudi, Charuvastra, & Ling, 2003).

### **COMBINATION TREATMENTS FOR ALCOHOL ABUSE & DEPENDENCY**

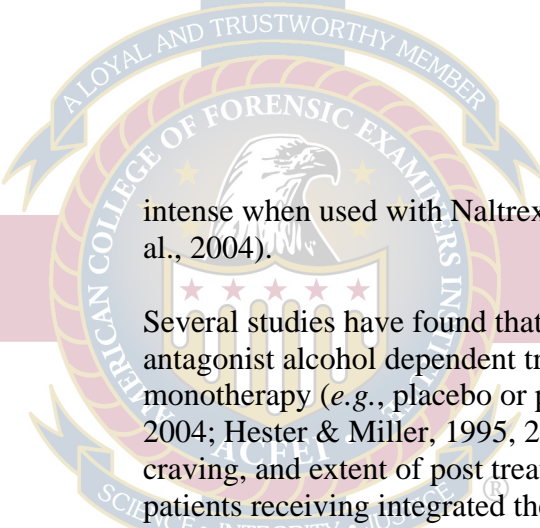
Because of the numerous interactions among neurotransmitters, combining therapeutic agents for the treatment of alcoholism may prove to be the most effective strategy. One potentially promising treatment would be to combine Naltrexone and Acamprosate (Kiefer & Wiedemann, 2004). Naltrexone reduces the craving produced from alcohol's positive reward effects (Volpicelli et al., 1995) and Acamprosate diminishes craving associated with the period following acute withdrawal (Spanagel & Zieglinsberger, 1997). Johnson & Ait Daoud (1999) summarize that the combination of Naltrexone and Acamprosate might not only make it easier to abstain from alcohol use but also might more effectively prevent a "slip" from turning into a relapse (consuming five or more drinks). Patients who use a combination of Acamprosate and Naltrexone have a better outcome than those who take either drug alone (Kiefer, Jahn, & Tarnaske, 2003). Swift (1999) commented that alcoholics who receive Acamprosate and concurrent psychosocial therapy demonstrated increased rates and duration of abstinence; again, however, with little impact on cravings.

When treated with Naltrexone and medication management, or Naltrexone with cognitive-behavioral intervention, the later had the most significant impact on remaining abstinent (Anton et al., 2003). The use of Naltrexone also reduced the risk of a heavy drinking day, and even more so over time in the group receiving Naltrexone and medication management versus cognitive-behavioral intervention. In addition, O'Malley et al. (2003) found that Naltrexone used in conjunction with primary care management or cognitive-behavior treatment yielded significant abstinence maintenance.

Jaffe, Rounsaville, Chang, Schottenfeld, Meyer, & O'Malley (1996) found that Naltrexone increased abstinence among patients assigned to receive supportive psychotherapy but not among those assigned to psychotherapy designed primarily to increase coping skills. However, for patients taking Naltrexone who drank, those who received coping-skills training were less likely to drink heavily than those who received supportive therapy. Over 85% of study participants increased days of abstinence and decreased drinking days when combining Naltrexone and medication management (Anton et al., 2008).

Naltrexone, in conjunction with counseling, has also been found to be effective in maintaining abstinence and the behavioral or counseling intervention do not need to be





intense when used with Naltrexone (O'Malley et al., 2008; Anton et al., 2006; Kranzler et al., 2004).

Several studies have found that patients receiving integrated psychosocial and Opioid antagonist alcohol dependent treatment had outcomes superior to those receiving monotherapy (*e.g.*, placebo or psychosocial treatment without meds) (Vaughn & Howard, 2004; Hester & Miller, 1995, 2002). Rates of relapse, levels of self-reported alcohol craving, and extent of post treatment alcohol consumption were significantly reduced in patients receiving integrated therapy. However, the long-term efficacy of integrated psychosocial and Opioid-antagonist dependence treatment was not established. In addition, integrated therapies also include reductions in the average number of drinks per day, proportion of total days spent drinking, and time to first heavy-drinking episode.

Vaughn & Howard (2004) also found that when treatment ended there was a corresponding diminution of treatment gains. This suggests that long-term administration of Opioid antagonists may be justified given the nontoxicity and efficacy of these agents. Volpicelli et al. (2001) proposed a case management-based integrated treatment approach.

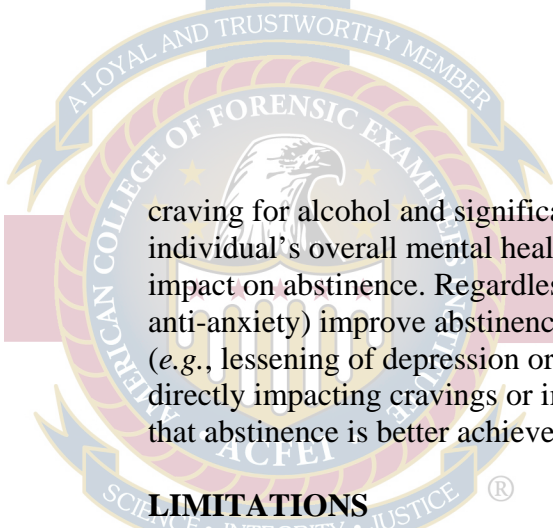
O'Malley, Jaffe, Chang, Schottenfeld, Meyer, & Rounsaville (1992) found that abstinence was highest for both males and females who used Naltrexone along with generalized supportive psychotherapy (psychosocial treatment involving individual coping skills/relapse prevention therapy or supportive therapy without a specific coping component). However, the combination of Naltrexone and a more intensive therapeutic program designed to teach specific coping skills was far more effective at preventing relapse among patients who sampled alcohol. They also found that among patients who sampled alcohol during treatment, who had received Naltrexone and coping-skills therapy were least likely to relapse.

Fuller & Hiller-Sturmhofel (1999) discussed the impact of Alcoholics Anonymous in the treatment of alcoholism. They cited the impact of a study that showed that found that patients who attended Alcoholics Anonymous without any other treatment intervention fared far worse than those who attended more structured treatment interventions (Walsh, Hingson, Merrigan, Levenson, Cupples, Heeren, & Coffman et al., 1991).

Chick et al. (2000) found that patients who had full attendance in a treatment program and compliance with Naltrexone demonstrated a reduction in total alcohol consumption and greater reduction in craving. However, time to first heavy drinking episode was not found in this study and one explanation for this is that the treatment program may have been less intense than the treatment programs reported in other studies. Patients compliant with Naltrexone had the highest overall treatment effects (Chick et al., 2000; O'Brien et al., 1996; Volpicelli et al., 1997). There was no Naltrexone effect found for the less compliant patient.

It appears that medications that are used to treat various mental health concerns (*e.g.*, depression, anxiety, seizure disorder) have been shown to be effective in decreasing





craving for alcohol and significantly improved abstinence rates. Certainly improving an individual's overall mental health and self-esteem would be expected to have a positive impact on abstinence. Regardless of whether the medications (*e.g.*, anti-depressants or anti-anxiety) improve abstinence rates because of their impact on the identified symptom (*e.g.*, lessening of depression or anxiety) or because of their psychopharmacologic effect directly impacting cravings or impacting alcohol's effect on the brain, the end result is that abstinence is better achieved.

### **LIMITATIONS**

Not all studies demonstrated the positive effects discussed above. However, most studies that failed to support the above data presented with experimental flaws or limitations, involved ineffective dosages, or involved confounding mental health or substance abuse scenarios. In addition, information was provided about the subjects involved in the above cited studies but was not included here. This was a thorough but not exhaustive review of the literature of medication used in the treatment of substance abuse and dependency.

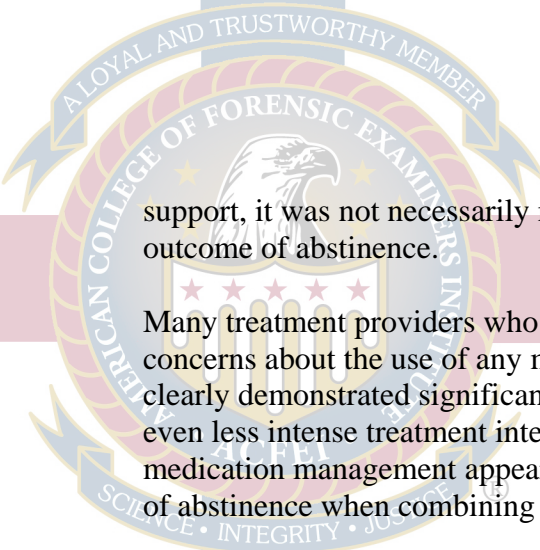
### **DISCUSSION**

The traditional treatment and management of substance abuse involved group treatment and attendance at Alcoholic Anonymous (AA) meetings. There were many misperceptions about substance abuse, perhaps the most significant being that substance abusers were "powerless" in dealing with their addictions and cravings. Well, that certainly does not appear to be the case. With or without professional help it is likely true that many substance abusers would be able to achieve and maintain abstinence. The use of medication has been proven to be an important and effective adjunct for substance abuse intervention.

### **SUMMARY**

It was not that long ago that it was believed that substituting one medication for another (*e.g.*, alcohol for Antabuse or an antidepressant) was not recommended. However, we have come a long way in understanding the integrated problem of neurobiology and substance abuse. Two medications have demonstrated significant impact for achieving abstinence and ending abusive drinking. Acamprosate (*Campral*) has been shown to decrease the intensity of craving after a person has stopped drinking as well as to help decrease the intensity of the cravings in general. Naltrexone (*ReVia*) has been shown to reduce drinking and increase abstinence by reducing the positive reinforcing, pleasurable effects of alcohol. The time has come to invest in what appears to an effective substance-abuse course of treatment.

Naltrexone, Acamprosate, and the combination of both were superior to placebos. In addition, Naltrexone alone was superior to Acamprosate alone, but again, the combination of both medications produced the strongest gains for sobriety. In addition, the combination of both Naltrexone and Acamprosate were associated with improvements in other treatment outcome measures, including the number of days and decreased cravings (as discussed in Johnson, 2007, chapter 19). Overall, the majority of the research appears to support that the use of Naltrexone, Campral, and some type of therapeutic intervention. Though cognitive-behavioral intervention appears to have strong

The seal of the American College of Forensic Examiners Incorporated is located in the top left corner. It is a circular emblem with a blue outer ring containing the text "A LOYAL AND TRUSTWORTHY MEMBER". The inner ring is gold and contains the text "AMERICAN COLLEGE OF FORENSIC EXAMINERS INCORPORATED". The center of the seal features a shield with a white eagle perched on a branch, surrounded by five stars. Below the shield, the words "SCIENCE • INTEGRITY • JUSTICE" are written in a blue arc.

support, it was not necessarily more effective than other therapeutic approaches in the outcome of abstinence.

Many treatment providers who treat substance abuse and substance dependency have concerns about the use of any medications in treatment. However, the literature has clearly demonstrated significant benefit not only for the use of medications, but perhaps even less intense treatment interventions. Cognitive behavioral interventions and medication management appear to have very similar positive impacts for the maintenance of abstinence when combining the appropriate medication.

In the forensic field we often have to continue to educate the public and professions that no one is ever “out of control” when it comes to their criminal behavior nor their continued use or abuse of drugs or alcohol. Perhaps the substance abusers need to be held accountable for their actions regardless of whether they were intoxicated or impaired. If they sincerely desire and work at sobriety, they will likely succeed. Medication and cognitive-behavioral interventions will increase the success rates. If the substance abuser believes that they are powerless or that their use of alcohol or drugs make them somehow not responsible for their behavior, then they have little if any chance at success. We have effective interventions for substance abuse and must hold the substance abuser accountable for their successes and failures.



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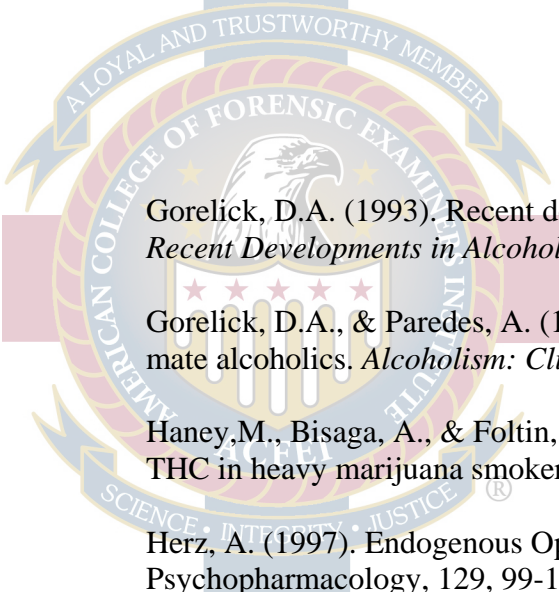
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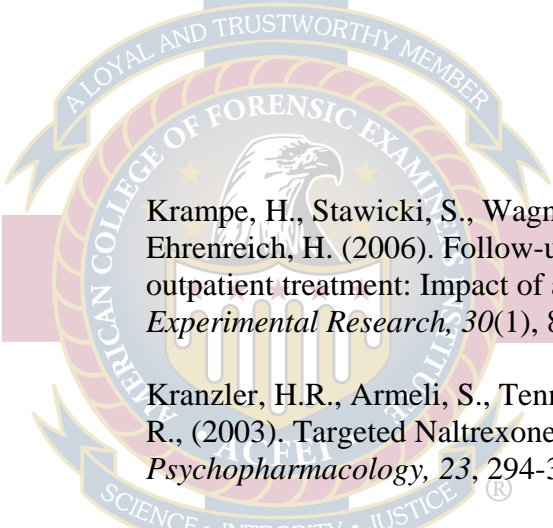
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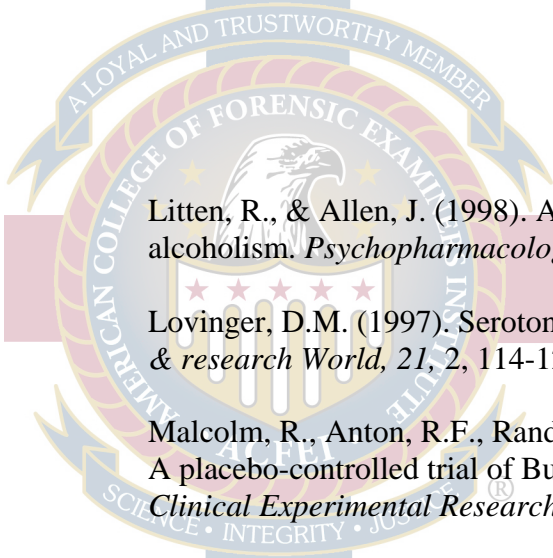
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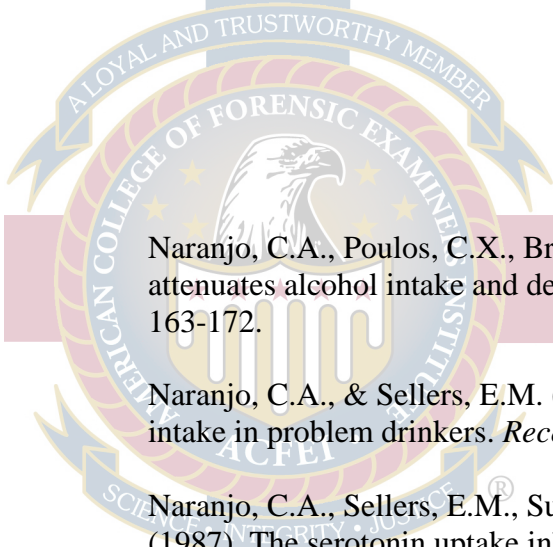
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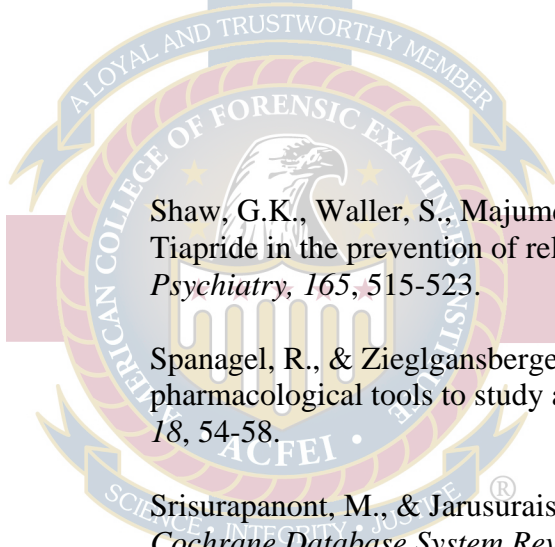
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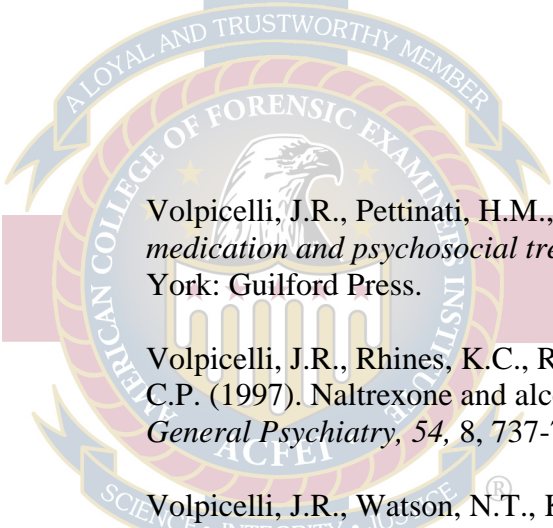
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### Learning Objectives

After studying this article, the participant should be able to do the following:

- 1) Understand the importance of utilizing anticraving medication to treat substance abuse.
- 2) Explain the benefits and outcomes of utilizing naltrexone and acamprosate with cognitive-behavioral treatment interventions.
- 3) Understand what the research has to say in support of anticraving medication.

### Target Audience:

Substance abuse treatment and assessment personnel; Forensic Psychologists.

Prerequisites: None

Program Level: Basic

