Opioid Antagonists in the Treatment of Impulse-Control Disorders

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Background: Symptoms of impulse-control disorders are generally refractory to psychotherapeutic or pharmacologic treatments. Recent study results suggest that opioid antagonists may reduce human urges, one of the core symptoms of impulse-control disorders. The author discusses the rationale for and the potential utility of the opioid antagonists in the treatment of impulse-control disorders.

Method: Work by preclinical and clinical investigators on the subject of motivation and its contextually relevant behavior is reviewed. The review includes the pharmacologic modulation of the motivation or drive and subsequent changes in behavior in animals and humans. On the basis of these reviews, the author prescribed naltrexone for up to 9 months to 15 patients who had impulse-control disorder, and 3 select cases are reported.

Results: Naltrexone was generally well tolerated, and there were no hepatic side effects. Naltrexone appears to reduce urge-related symptoms and decreases the problematic behaviors such as pathological gambling. The effect appears to be sustained. In general, 50 mg/day of naltrexone was not effective. Most patients required higher doses. Results were similar in the 12 other cases not reported here.

Conclusion: Naltrexone may be of use in select impulse-control disorder patients. Other opioid antagonists such as nalmefene also need to be tested. Until controlled study data become available, the present report should be viewed as preliminary.

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Naltrexone is a long-acting opioid antagonist whose efficacy has been tested in bulimia nervosa,[1–4] alcoholism,[5–7] borderline personality disorder with self-injurious behavior,[8,9] drug abuse,[10–13] obsessive-compulsive disorder (OCD),[14–16] mental retardation with self-injurious behavior,[17,18] and other psychiatric disorders.[19,20] Both positive and negative efficacy data have been reported except in alcoholism, in which the efficacy has been established.[5–7] The overall impression within the research and clinical community is that naltrexone is not highly effective in most of these disorders.

A major problem underlying most of these disorders is one of urges. The urges are usually the beginning symptoms and also the primary driving forces behind a motor or behavior program that is designed to relieve the underlying tension and/or generate pleasure temporarily. Patients who responded to naltrexone treatment often reported that symptom relief emerged in a relatively short period of time.

Since drugs that treat the beginning symptoms in a disease cycle tend to bring about quicker and more complete symptom relief than drugs that work on the secondary symptoms, one of the primary reasons for the improvement in these disorders was suspected to be due to the reduction of urge symptoms brought on by naltrexone. In one study, naltrexone was shown to reduce urge symptoms associated with alcoholism.[21] Because addiction patients often complain of strong urges, initial attention was directed toward the relationship between drug abuse and urges.

In recent years, drug addiction researchers have narrowed their attention to the ventral tegmental area-nucleus accumbens-medial orbital frontal cortex (VTA-NA-mOFC) circuit and attributed the neural substrates for the drug-induced hedonic experience and drug withdrawal symptoms to this region.[22–28] More recently, investigators began to report separate neural processing areas for the food-related liking (pleasure) and wanting (urges) within the VTA-NA-mOFC and its extended circuit (for a review, see reference 29). The cells within the orbital frontal cortex are capable of responding to a positively reinforcing stimulus in a highly discriminating manner, whereas the cells in the lateral hypothalamus, the substantia innominata, and the amygdala are not as selective in their response to a reward stimulus.[30] The results of 2 recent human positron emission tomography (PET) studies

also demonstrate a positive correlation between the severity of urges and increased glucose metabolism in the orbital frontal cortex and its connected subcortical regions.[31,32]

In parallel to this addiction research, a group of preclinical investigators has broadly defined the relationship between a drive state and the behavior that is contextually relevant to the underlying drive.[33] Through a series of studies, these investigators demonstrated evidence of a functional link between the VTA-NA-mOFC and limbic motor circuits. These studies provide clues as to how a drive or motivational state may propel an organized behavior that is designed to fulfill underlying desires or urges.[33,34] Although intriguing, these preclinical findings have not been tested in any meaningful way in clinical populations.

Within DSM-IV, intermittent explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania are grouped as impulse-control disorders. Compulsive shopping and each of the above descriptive diagnoses describe problematic behaviors that are triggered by uncontrollable underlying urges. Urges, however, have not been defined as the primary problem. Instead, they have been viewed as 1 of the symptoms of each disorder. Thus, it is proposed that in impulse-control disorders the primary problem is uncontrolled urges, and the pattern of expression of the urges dictates each descriptive diagnosis. It is also theorized that resolution of the urges will bring about the resolution of the rest of the behavioral symptoms of impulse-control disorders.

These views have led to the search for a pharmacologic means of reducing urge symptoms. The problem was approached based on the preclinical data that demonstrated a link between a drive-state or drug-seeking behavior and the VTA-NA-mOFC region (see above). Thus, the interest was focused on the compounds that modulate functions within this system. Since 1 of the major pharmacologic actions of naltrexone (or 5-HT_3 antagonists) is the inhibition of dopamine release in the nucleus accumbens through the disinhibition of γ-aminobutyric acid (GABA) input to the dopamine neurons in the ventral tegmental area,[35–44] it was reasoned that naltrexone may have a role in impulse-control disorders. Modulation of drive and subsequent behavioral output by dopamine, endorphin, and GABA have been studied extensively, but the specific mechanisms are still not well understood.[24,33]

Previously, some, but not all, naltrexone clinical studies have shown efficacy in the treatment of psychiatric disorders in which the primary problems were urges. In these studies, investigators invariably implicated increased endorphin levels or endorphin receptors in a given disorder or a pain mechanism. It was not clear as to how and where in the brain endorphin levels were exerting their effects. In the present proposal, the efficacy of naltrexone in urge-related disorders is attributed in part to the reduction of urge symptoms brought on by naltrexone through its action in the VTA-NA-mOFC circuit. The reasons for coming forward with this proposal are 3-fold. First, the preclinical data demonstrate that the reward, place conditioning, and drug withdrawal symptoms are modulated by the 5-HT_3 receptor and opioid antagonists at the mesolimbic region.[22–29] Second, a PET study by Volkow and colleagues[31] demonstrates that there is a significant correlation between cocaine craving and increased glucose metabolism in the VTA-NA-mOFC (specifically, medial orbital frontal cortex). Third, previous clinical naltrexone treatment studies in an urge-driven disorder suggest that naltrexone reduces urges in humans.[21] Naltrexone has not been tested in impulse-control disorders. Historically, these disorders have been considered refractory to known pharmacologic or psychotherapeutic treatments.

PRELIMINARY CLINICAL TRIAL

A brief naltrexone treatment experience is described below for 3 select cases from a group of 15 patients with impulse-control disorder. Each patient was treated with naltrexone for up to 9 months; results were similar in all patients.

Patient 1: Pathological Gambling

A 55-year-old man presented with severe pathological gambling and compulsive shopping symptoms. The patient had lost $50,000 during the past 3 years. At 50 mg/day of naltrexone for 2 weeks, the patient reported no change in his symptoms. Within a few days after the naltrexone dose was raised to 100 mg/day on his second visit, the patient reported:

> My most serious problem was gambling. I was addicted to the lights and chatter and other noises of the casino. It helped me get out of myself. If I had money to gamble, I would start mental play while I was driving to the casino. Once I parked the car, this mental play took on a high fever. By the time I walked into the casino, my breathing was real shallow and quick, and I am almost trembling and shaking over the excitement created in my mind. Now the gambling and buying urges are lifted, and I feel like I am a new man. All that mind play about gambling and hoarding and guilt and other emotional stresses is gone. I went up to collect payment on my land, and it was given to me in cash. If it would have been 2 months ago, I would have burnt the tires of the car getting to the casino. Instead, because of naltrexone, I drove sensibly to the casino. I was about to test myself. I parked the car, took 4 or 5 steps to the casino, and noticed my mind was clear. I was not calculating and strategizing and breathing shallow. As I walked to the casino my excitement wasn't there. I entered the casino, and I felt like I was in a grocery store. I walked past many machines and didn't put in one coin. I didn't have the urge to put in the coins. I did not feel like I was tempted and warding off temptation. It's a miracle.

The patient reported that he has not spent one dime for the past 9 months and has auctioned off his hoarded junk.

Patient 2: Compulsive Shopping

A 46-year-old woman reported a 7-year history of bulimia nervosa symptoms and a 5-year history of compulsive shopping. Compulsive-shopping symptoms were her chief current complaint. Shopping symptoms had ruined her financial condition. She had 11 binge/purge cycles per week, suggesting that her bulimic symptoms were also severe. She had a long history of cocaine and narcotics abuse but managed to overcome her problem through a series of chemical dependency treatments.

Her beginning naltrexone dose was 50 mg/day. She developed diarrhea and nausea. These side effects subsided in 1 week. She did not report symptom improvement. At week 2, her naltrexone dose was raised to 100 mg/day. She tolerated this dose well. Her shopping symptoms decreased significantly within several days. She said she no longer was developing elaborate plans or routes to attend sales. Incidentally, her binge/purge cycles decreased from 11 per week to 1 per week initially, and presently, she no longer has binge/purge symptoms. She reported a substantial decrease in her urges to shop and binge. The symptom relief has been sustained for the past 7 months. Results of liver function tests are normal.

Three other patients who are compulsive shoppers have also responded well but are not reported here.

Patient 3: Kleptomania

A 38-year-old woman presented with severe washing and hoarding symptoms. Her symptoms started during high school and had been refractory to treatments given by OCD drug and behavior specialists in and out of the state. She also had an uncontrolled stealing behavior. Whenever her mother accompanied her to a shopping center, the mother would witness the stealing behavior. The mother was afraid that her daughter might end up in jail eventually.

Urges to steal toys and dolls did not change at 50 mg/day of naltrexone for 1 week. When the naltrexone dose was raised to 100 mg/day, she began to report clinically significant decreases in stealing urges within several days. At 150 mg/day, she no longer had stealing urges. After 6 weeks of treatment, she stopped taking naltrexone because of the side effects (patient described these as flu-like symptoms that included chill, myalgia, and arthralgia). Within a few days, her stealing behavior returned. She described the urges to steal as irresistible and uncontrollable. She requested to go back to naltrexone (150 mg/day) and once again noted the symptom relief. Because of the recurring flu-like symptoms she had to stop naltrexone once again. She has since been arrested twice. Her washing and hoarding symptoms have not changed. Results of liver function tests are normal.

DISCUSSION

Thus far, results from clinical application of naltrexone to pathological gambling, compulsive shopping, kleptomania, and bulimia nervosa suggest that there is a need for controlled studies to further test these preliminary findings. One important fact is that the dose has to be titrated upward until the effect emerges or when the symptoms recur. Once the optimal dose is reached, the effect seems to emerge within 1 week. Thus, it would be reasonable to increase the dose if there is no significant improvement within 7 to 14 days, assuming that the patient tolerates the drug. In most cases, the effect emerges at 100 to 200 mg/day. As stated before, this finding is consistent with preclinical data demonstrating that the pharmacologic action of the 5-HT_3 receptor and opioid antagonists at the mesolimbic region is dose-dependent.[38,40–42] The finding also perhaps explains why the low-dose studies have failed to demonstrate efficacy in previous clinical trials in which urges were the dominant problems. Because of a wide margin of a dose-response pattern, flexible- instead of fixed-dose studies are recommended until a minimum effective dose is established for each disorder. Since naltrexone poses a potential hepatic risk at higher doses, parallel nalmefene studies are also needed for the risk/benefit comparison.

The finding also illustrates the complexities of the pharmacologic mechanisms within the neural organization. Pharmacologically, 50 mg/day of naltrexone exceeds the plasma levels needed to saturate central nervous system (CNS) opiate receptors,[45] yet all patients showed improvement at a dose higher than 50 mg/day, which is the recommended dose for morphine dependence. Several recent controlled clinical naltrexone treatment studies that have used a 50-mg/day dose failed to demonstrate efficacy except in alcohol dependency.

Patients 1 and 2 illustrate how different urge-driven psychiatric disorders can occur together at the same time, or individually at different times. This finding also suggests that one day, with improved understanding of the pathophysiology, these disorders may be lumped rather than split, as is the case now. In patient 1, pathological gambling and compulsive shopping and, in patient 2, bulimia nervosa and compulsive shopping symptoms improved together. Why the behavioral expression pattern varies among individuals or at different times in an individual is not known. The afferent stimulus input, ontogenetic factor, and learned association may, alone or together, play a role in this behavioral expression pattern.

The present finding is consistent with earlier findings that naltrexone is effective in the treatment of alcohol dependence. More recently, Mason and coworkers[46] reported efficacy of 6-methylene naltrexone (nalmefene) in the treatment of alcoholism. Indeed, naltrexone may

also be effective in the treatment of other impulse-ridden disorders, such as paraphilia.

Because of the potential overlap between compulsive and impulsive disorders,[47–53] naltrexone was also tested in the treatment of obsessions; so far the effort has not been successful. Although the investigations have been limited in scope, others have also tested naltrexone in OCD and found no significant effect.[15,16] Disorders such as OCD, Tourette's disorder, and trichotillomania that have preponderant aversive symptoms (often triggered by an aversive stimulus in the case of OCD) and stereotyped motor signs may be mediated through a different circuit than disorders that trigger urges due to a positively reinforcing stimulus. Underneath the compulsive shopping, compulsive stealing, and pathological gambling behavior, there is the symbolic conjecture reminiscent of hoarding. Preclinical studies have shown that hoarding behaviors are primarily processed in the VTA-NA-mOFC circuit[54–58] and not within the OCD circuit. Hoarding symptoms that occur in some OCD patients have been shown to be refractory to the known OCD treatment.[59] The hoarding that results from uncontrollable urges to buy (compulsive shopping in patients 1 and 2) may respond differently to a treatment than the hoarding that comes from fear of throwing things away (OCD, patient 3). Interestingly, the VTA-NA-mOFC circuit [22–26] and the putative OCD circuit[60–65] are juxtaposed anatomically.

Impulsive and/or impulsive-aggressive behaviors have been attributed, in part, to a central disinhibition. The possible role of dopamine in the modulation of central disinhibition has already been mentioned. Additionally, in a series of studies, investigators have demonstrated links between the low serotonin function in the CNS and the impulsive aggressive behaviors.[66–69] These studies have suggested that frontal, especially orbital frontal cortex, glucose metabolism is inversely correlated to the cerebrospinal fluid 5-hydroxyindoleacetic acid levels. The findings suggest that decreased serotonin function within the defined CNS region engender disinhibition and may trigger the diverse impulse-control disorders. In support of these findings, the serotonin selective reuptake inhibitors (SSRIs) have been shown to be effective in reducing impulsive aggressive behaviors and are commonly prescribed by clinicians.[70–72] Most recently, Black and colleagues[73] have reported that fluvoxamine, an SSRI, is effective in the treatment of compulsive buying. Naltrexone has also been shown to be effective in the treatment of impulsive aggressive behaviors in some but not all studies.[8,9,17,18] Taken together, the evidence suggests that biogenic amines such as serotonin and dopamine modulate tonic inhibition within the frontal cortex and subsequently the expression of impulsive behaviors.

Although only preliminary evidence is presented, the presence of urge symptoms, especially urges associated with a positively reinforcing stimulus, seem to be critical for naltrexone to be effective. If and when an individual engages in an impulsive act, naltrexone seems to reduce the subjective experience of pleasure. This finding is consistent with findings by alcoholism researchers, but differs from that of drug addiction researchers, who argue that pleasure and craving reflect opposite ends of chemical or cellular mechanisms (for example, high or low dopamine levels within the neural system).[22,46]

The findings also suggest that the treatment effect in impulse-control disorders is sustained. Six patients have maintained improvement for many months. The primary goal of this paper, however, is not to claim efficacy but to suggest a need for controlled studies.

Because the behaviors themselves have built-in rewards, many patients who have impulse-control disorders may not be motivated to receive treatment. Thus, naltrexone's utility may be limited to those who are motivated to stop the behavior. Furthermore, addiction researchers have expressed concerns that alteration of dopamine function within the VTA-NA circuit might engender anergia or dysphoria.[74]

Specific μ-, δ-, and κ-opioid antagonists that are currently under preclinical investigation may provide further insights into the pathophysiology and management of impulse-control disorders, some of which pose a significant socio-forensic risk.

Drug names: fluvoxamine (Luvox), nalmefene (Revex), naltrexone (ReVia).

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