Outpatient Detoxification Completion and One-Month Outcomes for Opioid Dependence: A Preliminary Study of a Neuropsychoanalytic Treatment in Pain Patients and Addicted Patients

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The current practice in the United States is to maintain patients with opioid dependence on opioids. A case series approach was used to investigate the results of outpatient detoxification/opioid-free treatment using a neuropsychoanalytic paradigm. Detoxification involved a single dose of buprenorphine, adjunctive medications, and intensive neuropsychoanalytic psychotherapy. Depression, attention deficit hyperactivity disorder (ADHD), and nicotine dependence were treated with bupropion. Low-dose naltrexone was used to remedy hypothesized low endogenous opioid tone. In the study, 92% of subjects completed one week of detoxification. By self-report, 60% were still sober one month into treatment. When divided into a group who met the *DSM–IV* criteria for opioid dependence because of withdrawal, tolerance, and inability to cut down or stop opioid medications only (the "Pain Group") and a group who met more than these three criteria (the "Addicted Group"), there were significant differences in maintaining abstinence. In addition, the Addicted Group were much more likely to be depressed and to have borderline personality disorder. All cases of ADHD and all drug dream reports were in the Addicted Group. The conclusion of the study was that neuropsychoanalytic treatment of addiction (including complete abstinence from opioids and neuropsychoanalytic interventions) may be a viable approach to opioid-use disorder. Current *DSM* criteria for diagnosis of addiction to opioids may incorrectly include a subgroup who are unable to stop the drug only because of inability to endure the withdrawal syndrome. With the neuropsychoanalytic approach, they appear to tolerate withdrawal and stay off opioids. Further investigation is required to compare this neuropsychoanalytic paradigm to other treatments.

Keywords: detoxification; endogenous opioid; low-dose naltrexone; neuropsychoanalysis; opioid dependence; outpatient opioid detoxification.

Background

Detoxification from opioids tends to be associated with poor outcomes. For example, a National Institute of Drug Abuse Clinical Trials Network study found that for 234 outpatients treated with buprenorphine/naloxone, 29% of patients were still in treatment and sober at the end of detoxification (Ziedonis et al., 2009). In another outpatient study with 510 subjects using buprenorphine/naloxone for detoxification, 4% of subjects completed a 5-day procedure and 16% completed a 30-day protocol (Katz et al., 2009).

In keeping with these poor outcomes for opioid abstinence, many treaters now think that long-term opioid substitution is the best course of treatment for patients with a history of opioid dependence. For example, Wesson and Smith (2010) stated that "Consensus in the US does not favor detoxification as a primary treatment. The Center for Substance Abuse Treatment argued in 2004 that the preponderance of research evidence and clinical experience indicates that opioid maintenance treatments have a much higher likelihood of long-term success than do any forms of withdrawal treatment" (p. 169). Stotts, Dodrill, and Kosten (2009) have argued that "Agonist maintenance therapy is currently the recommended treatment for opioid dependence due to its superior outcomes relative to detoxification" (p. 1727).

This emerging consensus is developing in the context of dramatically increased opioid usage in the general population. Medical use of opioids in the United States has multiplied by a factor of 10 since 1990, and

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more than 3% of all U.S. adults are now maintained on opioid medications for pain (Okie, 2010). Patients whose addiction began with prescription of opioids for chronic pain made up 50% of new patients entering methadone maintenance by the late 1990s (Brands, Blake, Sproule, Gourlay, & Busto, 2004). Of 113 patients presenting to an emergency department for refills of opioid prescriptions, 81% had risk factors for opioid dependence: depression, anxiety, a history of substance abuse, panic attacks, and posttraumatic stress and personality disorders (Wilsey, Fishman, Ogden, Tsodikov, & Bertakis, 2008). In summary, more and more patients are becoming addicted to opioids. Once addicted, they may continue opioid maintenance for years or for life.

The problem of opioid dependence is complicated by the fact that patients become addicted subsequent to medicating for chronic pain (Ives et al., 2006). Because of their added motivation to use opioids, chronic pain patients are difficult to detoxify. For example, a study of outpatient detoxification with buprenorphine in pain patients was shut down by its institutional review board because none of the subjects in the detoxification arm of the study could complete detoxification (Blondell et al., 2010). However, the difficulty of weaning pain patients off opioids may not be sufficient justification for long-term use if other alternatives are available.

Rather than accepting that all patients who have opioid dependence must be maintained on opioids indefinitely, we have piloted a novel approach to detoxification that may be of value. In 2009 the first author created a neuropsychoanalytic Addiction Medicine Service at SUNY Upstate Medical University. This service has successfully treated patients with addiction to opioids in the absence of chronic pain. However, the service also has been designed to have an embedded Pain Service because many patients with opioid dependence complain that they "must" use opioids for pain treatment. Therefore, without a way to fully evaluate or treat pain complaints, it would be impossible to deal with this justification for opioid use. Further descriptions of the treatment will be discussed under the "Methods" section.

We have previously categorized interventions in a neuropsychoanalytic therapy as treatment that integrates neuroscience-based interpretations, psychoanalytic interpretations, culturally competent clarifications phrased in a twelve-step idiom, and medication interventions (Johnson, 2009). Neuropsychoanalytic interpretations are designed to address issues that are dynamically unconscious—such as craving for alcohol, cocaine, food, and men with whom to use cocaine—and issues that are descriptively unconscious—such as the fact that nicotine or cocaine use might provoke craving for hydrocodone. In the case where the neuropsychoanalytic interpretations are descriptively but not dynamically unconscious, the information is also used in subsequent psychoanalytic interpretations, such as, "You know that inhaling nicotine is likely to make staying off hydrocodone harder. Why might you continue one addictive drug while trying to stay off another?"

In neuropsychoanalytic treatment of opioid withdrawal, low opioid tone during withdrawal is a central consideration, which is addressed both in terms of the individual state of the patient and also in the nature of relatedness with the therapist. We suggest that persistent low endogenous opioid tone might be a feature for some patients (perhaps as a preexisting factor before opioid dependence, or as a result of opioid use), resulting in persistent pain, anxiety, depression, and difficulty with relatedness. This low endogenous opioid tone might be an underlying cause for the distinction between autonomous depression and this particular form of "substance induced mood disorder" (Dakwar et al., 2011).

Normal baseline opioid tone may be necessary for a basic sense of well-being, and opioids may have an antidepressant effect (Stein, van Honk, Ipser, Solms, & Panksepp, 2007). A body of affective neuroscience evidence suggests that we need the unconscious positive feedback of endogenous opioid stimulation caused by social interactions to continue to engage in social interactions (Panksepp, 1998). This neuroscience formulation in no way excludes the psychoanalytic concepts of childhood experiences being repeated in a transference relationship, as described in Johnson's (2010) psychoanalysis of a man with heroin addiction. The goal of our neuropsychoanalytic interventions for opioid dependence includes an attempt to stimulate endogenous opioid tone through two routes: both with low-dose naltrexone, as explained below, and with human relationships propitiated by neuropsychoanalytic interpretations.

This report describes a clinical case series of this newly developed neuropsychoanalytic treatment of patients who had been maintained on opioids, whether for pain or because of addiction. The questions were:

1. Can we do any better with detoxification, or will we find that the consensus opinions cited earlier are confirmed? Once addicted to opioids, is it better for physicians to maintain patients?
2. Is there a difference between patients who are maintained on opioids for physical pain and patients who are addicted to opioids?

3. What do we notice about patients who go through this process? Do they seem autistic when their dose of opioid is high? Do they become panicked during withdrawal, and, if so, is there anything we can do about it, or will they flee back to opioid use?

Methods

Treatment setting

University Hospital is the main teaching hospital for the State University of New York Upstate Medical School, located in Syracuse. It provides tertiary care for an area about 160 kilometers from east to west and 300 kilometers from north to south. A referral base was built by performing hospital consultations on patients with addiction or pain, and by having the first author give grand rounds regarding neuropsychoanalytic concepts of addiction, pain, and endogenous opioid function for pediatrics, internal medicine, neurology, orthopedic surgery, anesthesia, rheumatology, obstetrics and gynecology, and emergency medicine at University Hospital and at a number of hospitals in the region. This resulted in referrals for both addiction and pain. Referrals were both local and from the wider catchment area. Trea tment offices were located in the Psychotherapy Division of the psychiatry building.

Subjects

The period under consideration in reporting results started in October 2010 with University Hospital's Institutional Review Board (IRB) approving use of deidentified patient information after subjects signed an informed-consent form. The study closed at the end of January 2012. Therefore, the statistics available for patients seen on the Addiction Medicine Service for 2011 should be representative of the subjects whose outcomes are reported here.

In 2011, there were 2,570 outpatient visits. The Addiction Medicine Service performed 326 University Hospital consultations, including 100 to the emergency department. This breaks down to about 11 outpatient visits per day, including 1.3 new patients and 1.2 consultations. The payer mix was 50% private insurance, 31% Medicaid, 16% Medicare, 2% Workman's Compensation, and 1% self-pay, suggesting that about half our patients were working and half were on public assistance.

During the period considered, there were 450 initial evaluations performed. A total of 50% of the patients cited opioids as the main drug of choice; 31% cited alcohol as the main drug of choice; 19% cited other main drugs of choice, most commonly marijuana, cocaine, and benzodiazepines. This is a report of consecutive admissions of opioid-dependent patients who required detoxification at the start of their treatment. Every patient who was admitted to our outpatient service during this 15-month period, who signed an informed consent permitting their deidentified information to be used, and who underwent opioid detoxification at the start of their treatment, is included in this case series.

These results were further broken down into two groups. The first group was the only one to meet the *DSM–IV* criteria for Opioid Dependence (APA, 2000), by virtue of the following three criteria: tolerance, withdrawal, and inability to cut down or stop their opioid medications. These were Pain Service patients, who were almost universally grateful to have a way to come off their opioid medications, and thus they were categorized in the "Pain Group." The second group consisted of patients who were more commonly multiply addicted, using heroin, cocaine, and other illicit drugs. If they were only using opioid pain medicine, they would run out early, go to multiple providers to obtain more pills, or behave in life-threatening ways as part of their addiction. These patients were categorized in the "Addicted Group." Subjects were only included in this case series if they signed an informed consent. This resulted in there being 22 Pain Group subjects and 61 Addicted Group subjects.[1]

The age range of all 83 subjects in the entire group was 17–81 years, with a mean age of 38 years (*SD* = 15.23), and the gender distribution was 36 men and 47 women. The age range of the 22 Pain Group subjects was 26–81 years, with a mean age of 53 years (*SD* = 12.75), and the gender distribution was 9 men and 13 women. The age range of the 61 Addicted Group subjects was 17–60 years, with a mean age of 33 years (*SD* = 12.21), and the gender distribution was 27 men and 34 women.

Treatment personnel

The Addiction Medicine Service was run as a neuropsychoanalytic training service. An administrator took intake calls and coordinated appointments. The first author taught two groups of trainees, a full-time psychiatry resident on a two-month rotation and a

[1] This number is lower than the total intake of opioid-dependent patients because initially the service lacked a system to track whether subjects had signed their informed-consent form.

variable number of medical students, most commonly 4, on third-year psychiatry clerkship for six weeks. All received a one-hour lecture on the first day that included an explanation of free association; a description of Kernberg's set of interpretations (clarification, confrontation, defense interpretation, and transference interpretation; Kernberg, Selzer, Koenigsberg, Carr, & Appelbaum, 1989); and an example of how to interpret drug dreams (Johnson, 2001). The training in neuropsychoanalytic treatment continued with eight hours of a seminar that considered various neuropsychoanalytic, neuroscientific, and psychoanalytic papers about addiction. Trainees were taken to an open meeting of Alcoholics Anonymous early in their rotation. The goal was for the trainees to see what happens at 12 Step Meetings as part of understanding the recovery culture.

Pain Service

One afternoon per week was organized as a Pain Service. The psychiatry resident and medical students were joined by a pain fellow who was undergoing a year of additional training in pain management after a residency, most commonly in anesthesia or physical medicine and rehabilitation. Patients were referred for intractable pain complaints irrespective of whether addiction was thought to be a consideration.

Initial evaluation

New patients were required to bring with them a "sober support person"—anyone who cared about them. This requirement resulted in more honest histories, reaching out for help before arriving, having a second pair of ears to hear the proposed treatment plan, and the beginning of a social support system for recovery.

All new patients had a complete psychiatric evaluation that included the adult attention deficit hyperactivity disorder (ADHD) Self Report Scale and the SCID 2 borderline personality disorder screen, a Hamilton Rating Scale for Depression, and a Modified Mini-Mental Status Examination to look for cognitive impairment. A physical examination was performed with a focus on the sources of pain.

Tests were done to evaluate hyperalgesia as a possible indicator of underlying opioid-system dysregulation on the day the Pain Service met. The most common measure of opioid-induced hyperalgesia (OIH) is the CPT (Pud, Cohen, Lawental, & Eisenberg, 2006). The entire forearm is submerged in a tub of icewater, at 1°C, for as long as the subject can tolerate the pain. The duration of submersion becomes a semi-objective measure of pain sensitivity. For example, Hay et al. (2009) found that CPT mean time for control subjects was 31 s, whereas for subjects maintained on methadone for addiction, or treated with maintenance methadone or morphine for chronic pain, the CPT mean times were all 18–20 s. This indicates that subjects maintained on opioids are more sensitive to pain. The CPT was mandatory for pain patients and was also administered when possible to the opioid-addicted patients.

Initial evaluations were performed by a trainee. Then the trainee, patient, and support person would be joined by the first author. The case was presented, further information was elicited from the patient, and the sober support person was asked to provide input and feedback about the evaluation, diagnosis, and treatment plan. The support person was invited to call or come back with the patient at any time. Ongoing involvement of the support person was variable, from only the initial visit to coming to several of the subsequent meetings. These repeat visits were usually restricted to a few minutes so that the support person's presence did not interfere with the individual psychotherapy. A group therapy was offered to sober support persons. However, a tiny minority of support persons went to our group therapy—run by another member of the psychiatry faculty. Neuropsychoanalytic therapy was begun the next day.

Psychotherapy

The first author was present during all outpatient psychotherapy sessions for 5–20 min, depending on the number of patients being seen that hour, while the psychiatry residents and medical students spent a full 50 min. The first author might be considered the primary clinician, while residents and medical students functioned as neuropsychoanalyst extenders. The first author performed a combination of supervision and patient treatment during the time with the patients and their resident or medical student. The first author would model how to intervene.

Psychotherapy was daily for the first week of treatment, and then twice a week for the remainder of the treatment. Goals of treatment were achievement of abstinence, remission of any comorbid Axis I disorders, and engagement in a long-term process of recovery, most commonly frequent attendance at Alcoholics Anonymous or Narcotics Anonymous. Patients were usually anxious and vulnerable initially. The treatment was organized to put a "human envelope" around them: 12-step recovery, sober support person, and in-

tensive contact with the treatment staff. Patients who wanted longer-term psychotherapy were referred after initial stabilization.

Since relatedness was conceptualized as a core problem for every patient, difficulties in relatedness were brought to the attention of the patients from the beginning of treatment. Trainees were instructed to focus on relatedness. They were to listen to the news of the day politely and wait until the material began to show signs of intrapsychic conflict. Addiction was defined as the urgent wish to use the drug despite repeated harm. The denial system was defined as any idea that allows drug use despite the harm that ensues. Denial is a common unconscious defense deployed to allow the use of a drug known to be harmful, but avoidance, minimization, disavowal, and other defenses are common. The goal of the interventions was to help addicted patients understand their addiction, to address the denial system that might lead to relapse to opioid use, and to show patients how they became less emotionally related to the therapists during treatment.

Pharmacologic interventions

Patients who called for detox were asked to arrive in withdrawal. After the initial evaluation, if the addicted patient was found to be in opioid withdrawal, the patient and support person were sent to the University Hospital pharmacy for medications. When the patient and support person returned, a list of withdrawal symptoms was elicited. The patient took sublingual buprenorphine in front of the evaluator until the withdrawal symptoms went into remission, usually 24 or 32 mg.

Our approach for opioids follows a common detoxification strategy for alcohol of replacing a short-acting drug with an intense withdrawal syndrome by loading with a long-acting alcohol cross-tolerant benzodiazepine that attenuates the withdrawal syndrome. A one-page sheet of instructions described how to use detox medications. The first author's cell phone number was put at the top of the page with instructions, "Call day or night if you need help." The following five medications were taken as needed.

- *Clonidine 0.1 mg* three times a day as needed to oppose the noradrenergic hyperactivity of withdrawal. The symptom target was anxiety.
- *Dicyclomine 20 mg* four times a day as needed to oppose the acetylcholine-driven gut hyperactivity of withdrawal.
- *Chlorpromazine 50 mg* four times per day as needed for nausea or anxiety. This drug was seen as a complement to dicyclomine. It blocks dopamine receptors on the brain's chemoreceptor trigger zone that is responsible for causing nausea and vomiting when it receives messages from the gut. It is a major tranquilizer.
- *Trazodone 100–600 mg* as needed for insomnia. The main action of trazodone for insomnia has to do with opposing excitatory 5-HT2A serotonin, H1 histamine, and alph-1 adrenergic receptors.
- *Bupropion extended release 450 mg* used for at least one constituent of the commonly seen triad of ADHD, mood disorder, and nicotine dependence.

The single dose of buprenorphine approach used here was adopted from Kutz and Reznik (2001). It is quite different from the standard approach in the United States of shifting the patient to buprenorphine for a week or a month (Katz et al., 2009). We discarded that approach as conceptually flawed—making a patient physically dependent on buprenorphine ensures a long, miserable withdrawal syndrome that the patient must endure for about three weeks. We have found buprenorphine to be the opioid most difficult to detoxify patients from.

Medications were managed daily. Medications were taken more frequently than indicated above, or less frequently, or other medications were substituted according to patient response. Each patient's treatment became completely individualized. The withdrawal syndrome usually peaked about Day 5 and was mostly resolved by Day 7. The five medications above, or other medications that had been used for detoxification, could be continued if they were helpful, and otherwise were discontinued.

Methadone or buprenorphine dependence could not be addressed by the strategy of replacing a short-acting opioid with long-acting buprenorphine. For methadone users, methadone was tapered by 20 mg/day to 30 mg and was then stopped for five days with use of the five adjunctive medications above; finally, a single dose of buprenorphine was administered and the adjunctive medications were continued. For buprenorphine users, buprenorphine was simply stopped abruptly.

For patients with chronic pain, we demonstrated concern about the pain and recommended specific non-addictive approaches such as physical therapy, NSAIDs for inflammatory pain, tricyclic antidepressants and anticonvulsants for neurogenic pain, or referral through the pain fellows for procedures such as nerve blocks. We often asked the question, what is the pain trying to tell you? For example, we would often explain that arthritic pain was a result of asking

the body to bear too much weight. We had a patient handout with information about a "sober diet" that explained how to lose weight. The psychotherapy might take up the question of why the patient ate unhealthy food and did not exercise.

Use of low-dose naltrexone

Low-dose naltrexone was administered to eliminate a hypothesized core reason for relapse (Koob & Volkow, 2010)—the persistent pain, anxiety, and depression of low endogenous opioid tone. The idea of using naltrexone originated with Brown and Panksepp's (2009) suggestion that, "There is now increasing data that would suggest that a temporary blockade of opioid receptors with low dose naltrexone may lead to an upregulation of mood enhancing endogenous opioids, and hence perhaps dopamine activity, which may further promote positive frames of mind" (p. 333). Naltrexone was initiated once the most substantial withdrawal symptoms were over, usually on Day 7. Consistent with seeing endogenous opioids as a slow-moving hormonal system, patients were asked to build up to 4.5 mg and take that dose for two months before discontinuing it. Naltrexone was compounded at the University Hospital pharmacy since it comes in 50-mg tablets. The initial dose of naltrexone was 1 mg during the treatment period reported. Because of frequent patient complaints of significant withdrawal symptoms after taking 1 mg, the initial dose has now been reduced to 0.1 mg. The sensitivity of patients who have discontinued opioids to this low-dose naltrexone may indicate that their endogenous opioid tone had been corrupted by opioid exposure. Many patients who receive naltrexone for alcohol dependence can immediately tolerate doses of 50 mg (Garbutt, 2010).

Opioid-induced hyperalgesia

The developing literature on opioid-induced hyperalgesia may help us understand the plight of opioid-addicted individuals. There is no evidence that OIH is always reversible; it may not be for a substantial segment of individuals who have been maintained on exogenous opioids. For example, CPT times are still dramatically shortened in subjects who have been off opioids for five or six months (Prosser et al., 2008; Pud et al., 2006; Ren, Shi, Epstein, Wang, & Lu, 2009). Therefore, persistent low endorphin tone may be a driver of opioid-addiction relapse.

Normal controls on Addiction Medicine have an average CPT of 102 s, and 95% can hold their forearm in the icewater for at least 35 s. OIH was diagnosed either because of a CPT time under 35 s or based on a history of escalating opioid dose for increasing pain without a change in cause of pain.

Data analysis

Two main outcome measures were recorded: completion of detoxification and abstinence at one month. Patients were counted as detoxification completers if they reported abstinence and were still in treatment a week after their single-dose buprenorphine administration. Patients were counted as abstinent after one month if they were still in treatment, and there were absolutely no reports or signs of use of addictive drugs other than nicotine (no marijuana, alcohol, cocaine, etc.). Urine verification of patient self-report was not conducted, and it is not regarded as necessary on a service with prolonged observation during free association of patients during psychotherapy hours. We present the one-week and one-month sobriety outcomes with confidence intervals (CIs). These were computed using STATA 11.1.

Results

Effects of treatment

For all opioid-dependent patients, 76 of 83 completed detoxification (92%; 95% CI [83%, 97%]), and 50 of 83 (60%; 95% CI: [49%, 72%]) were known to be sober from all addictive drugs except nicotine at one month.

In the Pain Group, 21 of 22 subjects completed detoxification (95%; 95% CI: [77%, 99%]), and 18 of the 22 were known to be sober at one month (82%; 95% CI: [60%, 95%]) (see Figure 1). Of the Addicted Group subjects, 55 of 61 completed detoxification (90%; 95% CI: [80%, 96%]) and 34 of the 61 were known to be sober at one month (56%; 95% CI: [42%, 68%]).

The above results for the Pain Group include the following added exposition. The one patient who did not complete detox arrived in a paranoid state. He had been maintained on opioids since a horrific accident that left him wheelchair bound. He felt entitled to be maintained on opioid medications forever. We never gained a therapeutic alliance. He left in the middle of detox feeling angry and victimized.

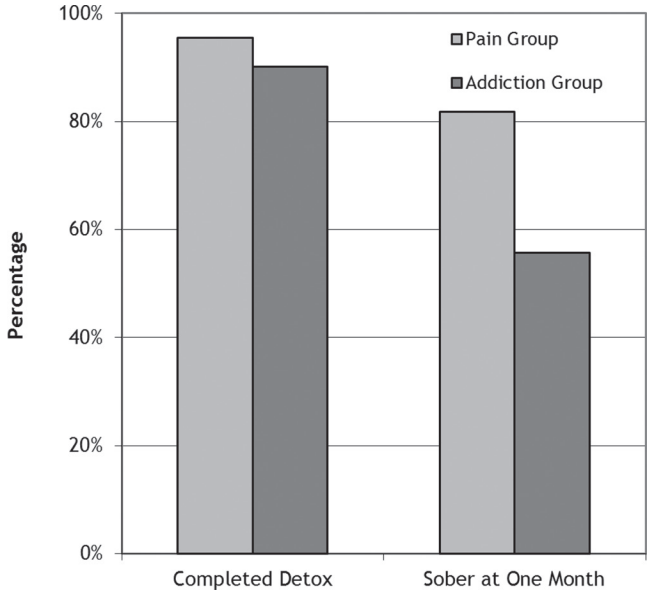

Figure 1. Outcomes of treatment.

Three Pain Group patients left treatment before they reached the one-month mark. Their attitude seemed to be, "Thanks. I'm happy to be off opioids. Coming here for more psychotherapy is not worth my time." Therefore, the one-month sober rate for this group may actually be as high as 95%.

Secondary measures

When comorbid diagnoses were assessed by group at initial evaluation (see Figure 2; statistics listed in Table 1), we found that there was a much higher frequency of depressive disorders among the Addicted Group (which decreased after one month of treatment). ADHD and borderline personality disorder occurred in a majority of the Addicted Group. Borderline personality was present in only one of the member of the Pain Group. The Pain Group was specifically selected for the presence of chronic pain, so all subjects in that group had chronic pain, but chronic pain was also present in half the members of the Addicted Group. Opioid-induced hyperalgesia was common in both groups, probably because of exposure to opioid suppression of pain drivers with secondary upregulation. Comorbid addiction to alcohol, cocaine, cannabis, and benzodiazepines was common in the Addicted Group, but not in the Pain Group. Nicotine dependence was much more common in the Addicted Group.

Drug dreams were exclusively seen in the Addicted Group (see Table 2). This interesting result suggests that somehow, despite significant opioid exposure in the Pain Group, the ventral tegmental dopaminergic SEEKING system (Panksepp, 1998) was not changed to produce opioid craving in this group (Johnson, 2001, 2003).

In summary, the Addicted Group demonstrated far more psychopathology than the Pain Group. In addition, sober outcomes for the Pain Group at one month were significantly better.

A result that we currently find unquantifiable has to do with a shift in the quality of relatedness during treatment. Whether addicted or not, patients routinely became more engaged, interactive, animated, and emotionally available during the course of treatment. This change was captured by the husband of one of our pain patients when he said, "I used to go do other things on the weekends because she slept all the time. Now I have the woman I married back." The word "autistic" might well characterize patients maintained on opioids—little interest in human interaction. The autistic behavior reverses with detoxification. Repeat pain scores were not measured, but detoxified subjects generally reported less pain after a month. Their pain lessened, and their interpersonal functioning improved.

One negative outcome was that a 19-year-old man, who completed one month sober from heroin and was discharged after two months of treatment, was found dead of a heroin overdose a month later. A death conference held with the treating staff, mother, and stepfather revealed the following negative factors. The patient adamantly refused to attend Narcotics Anonymous, saying that he would be fine without it. The patient had recently moved away from his mother and back in with his biological father, who had just been released from prison. The father had advised the patient to stop taking the bupropion, which had been so effective for his ADHD.

A second patient decided to experiment with "controlled drinking" during his psychotherapy, and he discuss the results with us. His parents came down for breakfast one morning to find him about to have a respiratory arrest. He had gone into an alcohol-induced blackout and bought heroin. An ambulance was called, and his respiratory arrest occurred on the way to the hospital. He recovered fully. The response of the service to these events is that since the outcomes reported here, new patients arriving with opioid dependence, and their support persons, each receive a rescue kit with which to inject naloxone into the quadriceps as part of responding to an overdose.

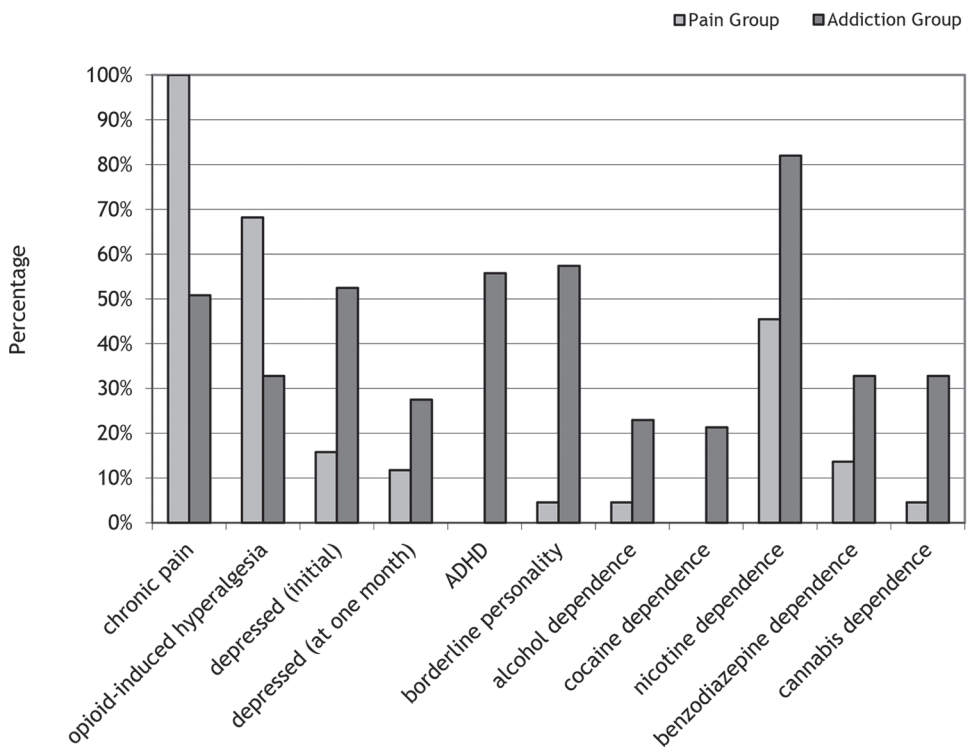

Figure 2. Comorbid conditions.

Table 1. Comorbid diagnoses by group

	Pain Group (N = 22)			*Addicted Group (N = 61)*				
Type of Patient	*No*	*Yes*	*% of total*	*No*	*Yes*	*% of total*	*p*	χ^2
Initially depressed[a]	16	3	16	29	32	52	.005	7.9
Depressed at one month[a]	15	2	12	29	11	28	.195	1.7
ADHD	22	0	0	27	34	56	.000	20.8
Borderline personality	21	1	5	26	35	57	.000	18.4
Chronic pain	0	22	100	30	31	51	.000	16.9
OIH	7	15	68	41	20	33	.004	8.3
Alcohol dependence	21	1	5	47	14	23	.054	3.7
Cocaine dependence	22	0	0	48	13	21	.018	7.8
Nicotine dependence	12	10	45	11	50	82	.001	5.6
Benzodiazepine dependence	19	3	14	41	20	33	.085	3.0
Cannabis dependence	21	1	5	41	20	33	.009	6.8

Note: Significance values calculated by Pearson chi-squared comparison with one degree of freedom. All measures indicate diagnosis at initial evaluation except for depression, which was also evaluated at one month. ADHD = attention deficit hyperactivity disorder; OIH = opioid-induced hyperalgesia.

[a] In the Pain Group, only 19 out of 22 subjects were included in the initial assessment of depression because the remaining three were concurrently in active treatment for mood disorder; 2 of those subjects did not complete the one-month followup and were not included in that measure. See text for details.

Table 2. Presence of drug dreams by group

	Pain Group (N = 18)			*Addicted Group (N = 56)*				
Drug dream	*No*	*Yes*	*% of total*	*No*	*Yes*	*% of total*	*p*	χ^2
Opioid dreams	18	0	0	34	22	39	.002	10.1
Alcohol dreams	18	0	0	52	4	8	.244	1.4
Cocaine dreams	18	0	0	51	5	9	.189	1.7
Cannabis dreams	18	0	0	52	4	8	.244	1.4
Nicotine dreams	18	0	0	53	3	5	.316	1.0
Benzodiazepine dreams	18	0	0	52	4	8	.244	1.4

Note: Significance values calculated by Pearson chi-squared comparison with one degree of freedom. All measures indicate diagnosis at initial evaluation except for depression, which was also evaluated at one month. Not all subjects were asked about drug dreams.

Discussion

The main finding was that this neuropsychoanalytic approach for detoxification of opioid-dependent patients has been shown to be relatively effective, based on a single case series. In addition to the success of the treatment in terms of detoxification and one-month abstinence, the contrast of the Pain Group and the Addicted Group revealed several features that merit further investigation as well:

- The *DSM–IV* criteria for opioid dependence were met by patients in the Pain Group, but they did not seem to be addicted. Rather, these patients seem stuck in a place where they could not stop taking their drug because the nature of the withdrawal syndrome is simply too difficult to negotiate. Given a means to go through withdrawal that was tolerable, this group appears to have been happy to give up their drug. Pain was consistently more tolerable after detox and a course of low-dose naltrexone. *DSM–V* (APA, 2013) criteria for Opioid Use Disorder would also be met by these patients. This suggests that future *DSM* criteria might account for this distinction between simple fear of withdrawal and opioid addiction as different underlying reasons for continued opioid use.
- The Addicted Group seems to have been dramatically sicker: depression, ADHD and borderline personality disorder were much higher in this group. The comorbid conditions probably contributed to their lower levels of abstinence and detox completion.
- 40% of the Addicted Group reported drug dreams, whereas none of the Pain Group reported drug dreams. Drug dreams may actually represent a change in the SEEKING system that is permanent, as described by Solms (2000). Our finding, while not definitive, provides more evidence that drug dreams may be used as a marker of a biological change in the brain that is pathognomonic for addiction, as we have previously discussed (Johnson, 2001, 2003).

We would like to highlight some aspects of our approach—as compared, for instance, to the Ziedonis et al. (2009) or Katz et al. (2009) studies—that we believe contributed to the effectiveness of the treatment. In our study:

- Patients were required to ask for help before arriving.
- The first focus of our treatment was on making a therapeutic alliance, with abstinence from all drugs as a shared goal of patient, sober support person, and treaters.
- Not admitting patients to a hospital for detoxification, and providing medical treatment in a psychiatric model where psychotropic medications were prescribed routinely by providers of psychotherapy, allowed for a seamless continuity of care rather than a need to switch providers from inpatient to outpatient facilities. During detoxification, patients made a powerful therapeutic alliance that carried them through the balance of the treatment. Although treatment was provided by physicians, the cost of treatment using this model is a fraction of that for one that requires inpatient admission. Although we are not able to estimate the exact savings in this study compared to inpatient admission, future work

should address cost comparisons of this regime with such treatment as usual.

- Buprenorphine was only given once. It may be that other detoxification protocols change physical dependence from a short- to a long-acting opioid, buprenorphine, and the protracted withdrawal created by this approach is less tolerable than our one-time dosing.
- Drug dreams were routinely interpreted as evidence of ongoing midbrain-based craving. One goal of treatment was to make patients aware that they had a lifelong brain disease.
- We asked patients to introspect about the effect of cigarette smoking on craving for opioids. A consistent neuropsychoanalytic interpretation was that it is difficult to use one intensely addictive drug, nicotine, and to stay off opioids (Stuyt, 1997).
- Typical of the neuropsychoanalytic stance, we helped patients be more conscious of both the biological processes that create craving and the hostility involved in using drugs. This hostility was often in evidence directly in the patient–therapist relationship.
- Therapists were taught to leave the agenda up to the patient and to make interpretations regarding difficulty with relationships directly in the room—not, "You seem to get angry at Aunt Sallie a lot," but, rather, "You seem to get angry at me a lot: tell me about that."
- We took a motivational interviewing-like stance regarding 12-Step programs as part of the treatment—for example, exploring with the patient the idea that, "Most people who have reliable recoveries go to NA or AA, why wouldn't you?" Treaters were quite interested in the answers and tried to understand the reluctance to engage in this valuable community resource.

As a summary, we can now answer the questions posed during the introduction.

1. *Can we do any better with detoxification, or will we find the expert opinions cited are confirmed? Once addicted to opioids, is it better for physicians to maintain patients?*

The findings reported here are preliminary evidence that there may indeed be a better way. In this case series of 83 subjects, 92% completed detoxification and 60% were known to be sober from all drugs except nicotine at one month. A repeated case series followed for a longer period of time is, of course, necessary to provide additional data, and controlled trials are ultimately necessary to evaluate the merits of this innovative approach.

2. *Is there a difference between patients who are maintained on opioids for physical pain and patients who are addicted to opioids?*

We suggest that the striking difference between the two groups may contribute to the development of more effective treatment going forward. Psychopathology was low in the Pain Group. None of them experienced drug dreams, hypothesized to represent a shift in functioning of the midbrain craving pathway (Johnson, 2001). Given these findings, we suggest that physicians should be more open to shifting patients from long-term opioid maintenance to alternative treatments. It appears that although physicians in the twenty-first century have become skilled at getting patients on opioid maintenance for chronic pain, they do not have good skills for reversing the process. Our findings represent a way for meeting the need to develop those skills, as many of these patients were grateful to have a way to get off opioids and, furthermore, found that their pain was reduced by the treatment. Whereas these patients had previously found the withdrawal syndrome punishing, frightening, painful, and intolerable when they tried to discontinue opioids, neuropsychoanalytic treatment offered a relatively benign experience. There was nearly complete adherence to treatment. Outcomes were good.

For the Addicted Group, things were more complicated. Drug dreams were common. Other drugs were commonly involved in the addictive illness. Borderline personality disorder and ADHD disorder both probably contributed to difficulty with the therapeutic alliance. Opioids seemed to be used to diminish the unpleasure of drug craving and to ameliorate problems with relatedness. The course of illness is affected by character functioning, which was less flexible, adaptive, and tolerant of discomfort for this group. However, given these challenging complications, we still found that detoxification completion and abstinence rates were high, suggesting that this treatment is also effective for patients with more entrenched motivations to continue using opioids.

3. *What do we notice about patients who go through this process? Do they seem autistic when their dose of opioid is high? Do they become panicked during withdrawal? If so, is there anything we can do about it, or will they flee back to opioid use?*

We did collect information suggesting that indeed the use of opioids had been associated with an "autistic"

stance (to be discussed in greater detail below), as comments from the patients and from their support persons indicated that there had been an avoidance of human contact during the period of opioid administration, which was then reversed with detoxification. For example, one woman said that she had spent several years mostly in her bedroom, where her focus was taking opioid pills prescribed for a supposedly disabling pain condition. She had been annoyed by comments her family made, such as, "Where is Jane?" During the treatment period, her father came in with her one day and remarked that she had called him from the supermarket asking if she could pick anything up for him while she was there, noting, "She hasn't called me in years!"

Some patients described a creepy feeling of social vulnerability and unease during withdrawal. The patients who did not complete their treatment seemed overwhelmed by their return to having relationships without exogenous opioid administration. However, it also seems that the use of neuropsychoanalytic interpretation may have directly counteracted this tendency, providing patients with more engagement and interpersonal contact through the deep inquiry provided in sessions, compared to more superficial questions like, "How is your pain?" which they may have encountered in other settings. This innovation in treatment, along with the immediate diagnosis and treatment of comorbid psychopathology, may have facilitated the outcomes described.

Limitations

The authors are aware that there are a number of limitations of the case series presented.

- There was no comparison group, such as a group receiving a different treatment approach.
- There was no independent verification of participant self-reports. We did not break the analytic frame of the treatment by asking for urine proof of veracity of self-report. However, we must note that many patients reported relapse, and they were continued in treatment without penalty. Using opioids was seen as evidence that addiction is a difficult disease, rather than failure of the participant, and reasons for relapse were explored as an aspect of the treatment. Therefore, while self-reports may have been inaccurate, there was no programmatic reason for patients to be dishonest. There was no penalty for using opioids or any other drug. Some patients were detoxified repeatedly, with constant psychotherapy regarding unconscious reasons for reinstituting use of a drug that had caused harm to them. Urine drug screens seem to be employed in other treatment models as part of community policing, collaboration with law enforcement officials, or to remove patients from treatment for relapsing—as if to punish them for being ill. Use of urine drug screens was reported by some patients to undermine their alliance with treatment and to promote a kind of cops-and-robbers contest to see if they could defeat the surveillance by hiding their drug use.
- The bulk of the treatment was provided by inexperienced psychotherapists with limited training, although this was mitigated by substantial treatment contact for all patients by the first author.
- Assessments were done by the first author/treater and other service providers rather than by an independent evaluator.
- The number of subjects in this clinical case series is small, because not all patients who entered treatment in our service were consented for inclusion in our IRB-approved outcome study; some were missed in the rush of clinical work.

A new metapsychology of endogenous opioid function

Having described a case series that indicates that a novel approach—integrating neuropsychoanalytic treatment with a low dose of opioid antagonism—and demonstrating a high degree of success in detoxification and abstinence, we would like to offer some thoughts as to the possibly underlying mechanisms of the success of this treatment and the previously existing opioid dysregulation the treatment may have targeted. We believe that our model illuminates why opioid dependence has been difficult to treat with an abstinence-based approach and why the outcomes reported above are relatively good.

Endogenous morphine, "endorphin," was first described in the 1970s (Snyder, 2004). Like a hormone, endorphin circulates through the blood to multiple receptor sites, affecting a number of physiological processes in the body and brain. Endorphin-containing leukocytes are part of the immune system (Rittner, Brack, & Stein, 2008). An important site of opioid receptors is in the gut. Exogenous opioid administration results in constipation. Withdrawal features symptoms of gut hyperactivity, including cramps, diarrhea, and vomiting.

A key function of endorphin is to ameliorate pain. For example, there is a sudden spike of endorphin

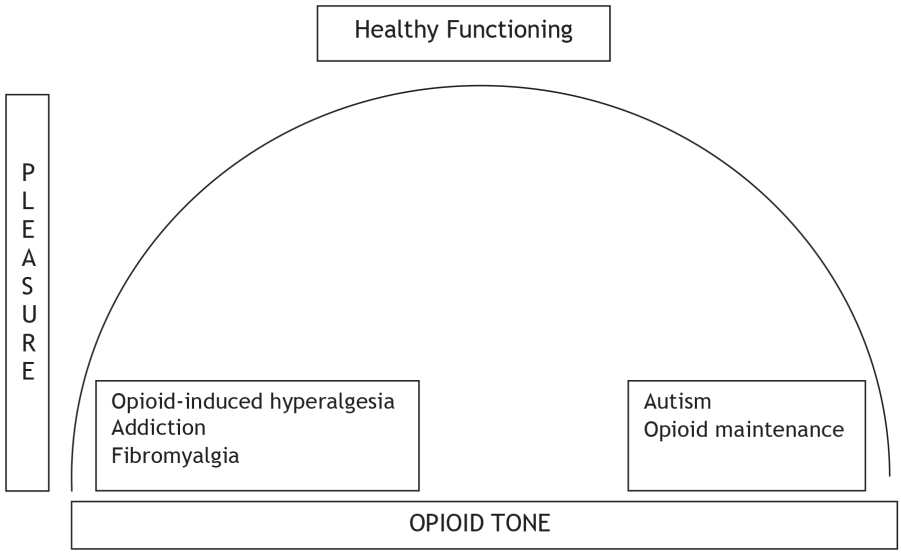

Figure 3. Metapsychological model: hypothesized relationship of pleasure and opioid tone in subcortical pathways.

production during labor (Brimsmead, Smith, Singh, Lewin, & Owens, 1985). It has been argued that this primitive analgesic function has been adapted in mammals to modulate social interactions (Eisenberger, Lieberman, & Williams, 2003; Stein et al., 2007). Furthermore, endorphin stimulation has been linked to pleasure (Robinson & Berridge, 1993) and is thought to be involved with basic well-being as well as positive social interactions, as opioid agonism and antagonism has a number of effects on social interaction (Panksepp, 1998).

Given this body of evidence, we have developed the metapsychological model represented in Figure 3. In the spirit of dual-aspect monism (Solms & Turnbull, 2002), we argue that endorphin can be measured objectively and can also be felt/introspected. At optimal levels of opioid stimulation (represented at the center of the graph), healthy individuals find pleasure in human interactions. We argue that we all unconsciously strive to keep endogenous opioid tone in this optimal zone.

This model may be illustrated with the following prototypical experience:

> If you haven't seen your children all day because you have been at work, you urgently want to play with them. Playing with them will bring your endogenous opioid tone from substandard (the left side of the graph in Figure 3) to optimal (top of the graph).
>
> Five hours later, after plenty of engagement, you need them to go to bed. Your endogenous opioid tone has overshot the peak. You are in the dysphoric zone (the right side of the graph). You want to sit quietly by yourself until your tone returns to the optimal level. This oscillation of opioid tone (represented by the bar under the peak of the inverse U) occurs in a narrow range.

Panksepp (1979) has suggested that when endorphin tone is too high, autistic behaviors result. In this condition, human contact "hurts." Autistic persons do not even want to look at others; it is too painful. Supporting this view are reports that blockage of endogenous opioids with high-dose naltrexone promotes social behavior (e.g., Leboyer et al., 1990; Panksepp & Lensing, 1991) and ameliorates autistic gaze avoidance (Lensing et al., 1995).

This model of dysphoria as a result of exceeding the midpoint of endogenous opioid function would explain why exogenous opioids are aversive for most people. One commonly hears from healthy people that they avoid opioids. One example of a randomized, double-blind study of intravenous ketorolac versus intravenous morphine for limb injuries (Rainer et al., 2000) showed that 5% of subjects had side effects from ketorolac while 89% complained of side effects from morphine, which was also less effective for pain. Sedation was complained of by 59% of subjects, 75% said they were dizzy, and 37% said they were nauseous. While both groups rated their satisfaction with management of the emergency department equally (a question to show that each group could be satisfied equally), satisfaction

with analgesia was significantly better for ketorolac than for morphine.

We would suggest that most healthy people are already optimizing endogenous opioid tone via frequent pleasurable human interactions. Exogenous opioid administration pushes these well-functioning persons into the autistic/dysphoric range. These individuals will avoid taking opioid medications with the possible exception of when suffering from intense pain. If an individual with normal relatedness suffers from chronic pain and begins taking maintenance opioid medications, he or she will begin functioning in the autistic spectrum of relatedness; human interactions will be avoided.

At the low end of endogenous opioid functioning, opioid-induced hyperalgesia, fibromyalgia, and addiction ensue. Putting these three disparate pathologies together is important conceptually, and it underpins our discussion of the empirical results reported in this article, because each pathology reveals a different aspect of endogenous opioid function.

Opioid-induced hyperalgesia, in which sensitivity to pain increases following chronic opioid administration, has been investigated using animal models, and its existence in humans is gaining acceptance (Huxtable, Roberts, Somogyi, & Macintyre, 2011). Mu-opioids are subject to multiple modulators: dynorphin (an opioid whose function appears to be antagonistic to mu-opioids), corticotrophin-releasing factor (CRF; Koob & Volkow, 2010), glutamate, and substance-P (Chu & Angst, 2008). As seen in Figure 4, which describes the "opponent process" in the central nervous system, a single dose of opioid provokes the "a" process—a reduction in pain, anxiety, and depression. The brain responds with the "b" process, increasing drivers of pain, anxiety, and depression such as dynorphin, CRF, glutamate, and substance-P to reestablish sensitivity to inputs such as pain that maintain tissue integrity. There is an overshoot of the b process. When given for chronic pain, opioids gradually exacerbate the pain because of the brain's b process, making the recipient of opioids increasingly pain-sensitive.

The value of considering the neuroscience underlying opioid-induced hyperalgesia becomes evident when combining it with psychological determinants of opioid addiction, which is thought to be related to the involvement of mu-opioids in reducing psychological distress. Opioid administration stops distress vocalizations in young animals separated from their mothers (Panksepp, 1998), and it probably also corrects the distress of inability to form safe relationships in humans. For example, in the first author's case report of the psychoanalysis of a man with heroin addiction (Johnson, 2010), annihilation anxiety entered the transference when the patient stopped using heroin during the psychoanalysis. The underlying childhood vulnerability had to do with repeated abandonments, beginning when his parents separated, followed by his mother leaving him at an orphanage when he was 2 years old. Repair of the ability to effectively modulate interpersonal distance, conducted within the transference relationship, resulted in sustained recovery from opioid addiction over the 9-year follow-up period.

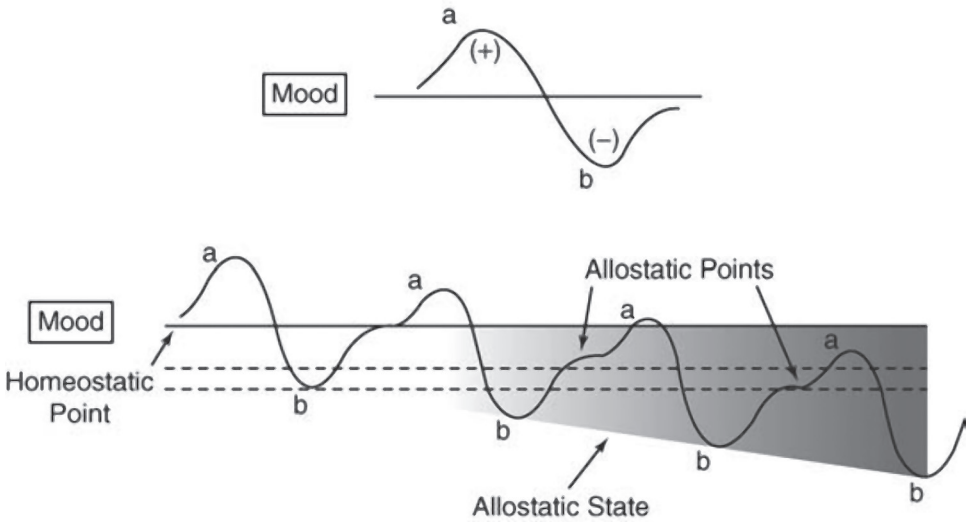

Figure 4. The "opponent process" in the central nervous system. (Reproduced by permission of Elsevier Science Inc., from G. F. Koob & M. Le Moal, "Drug Addiction, Dysregulation of Reward, and Allostasis," *Neuropsychopharmacology,* Vol. 24, 2001, pp. 97–129. © 2000 American College of Neuropsychopharmacology.)

Prescription opioid abuse, to the extent that it is addressing this aspect of opioid activity, might be described as, "A person in a pill." One patient remarked, "You know that feeling you get in your heart when you are in love? That's how I feel when I take an Oxycontin." From this perspective, only individuals who have difficulty obtaining satisfying endogenous opioid tone from human relationships would be vulnerable to becoming dependent on opioid self-administration to feel "good."

Combining the concepts of opioid addiction as an attempted solution to feeling calm/related via the use of exogenous opioids, and the concept of opioid-induced hyperalgesia as a condition where chronic opioid administration results in an overshoot of CRF, glutamatergic, dynorphin, and substance-P as well as other, currently unknown drivers of the "b" process, opioid-addicted individuals would be hypothesized to move from a state where exogenous opioids fix their dysphoria to a state where the dysphoria is never-ending. Each dose of exogenous opioid would help temporarily, but the overall trend of pain, anxiety, and depression would continue to worsen as the system adjusts to increased levels of exogenous opioids (Figure 4). The person is conscious of the "a" process—every dose of opioid helps with pain, anxiety, and depression. The person is not conscious of the "b" process; the brain rebels against opioid agonism by increasing the neurochemical drivers of pain, anxiety, and depression. Trapped between use of a drug that insidiously causes an increase of dysphoria and discontinuing the drug and suffering the withdrawal syndrome features of unmodulated pain, anxiety, and depression (inability to feel the presence of others via endogenous opioid tone), there would be a potent force militating towards persistent use of the exogenous opioid.

We suspect that a low-opioid state can also be induced by an autoimmune reduction in central nervous system tone and that this is the cause of fibromyalgia (Ramanathan, Panksepp, & Johnson, 2012). The cardinal symptom of fibromyalgia is generalized pain. There are 18 classic "trigger points" that are often found (Wolfe et al., 1990). These points are situated at oddly random points on the body, such as the fat pad on the inside of the knee. In addition to generalized pain, common coexisting findings include "fibrofog"—difficulty thinking—and an odd state of unrelatedness (Smith & Barkin, 2010) that makes fibromyalgia patients difficult to treat. Fibromyalgia has a definite gender unevenness—5% of women, 1.5% of men (Neuman & Buskila, 2003)—which reflects the 3:1 female/male ratio seen in autoimmune diseases. Comorbid psychiatric disorders are common in fibromyalgia. Of patients with fibromyalgia, 75% have a mood disorder, 60% have an anxiety disorder, and 26% have a substance-use disorder (Arnold et al. 2006). Fibromyalgia patients are most commonly treated with exogenous opioids (Berger et al., 2010), although there is no evidence base that this treatment is effective.

In autism, endogenous opioid tone is too high. In fibromyalgia, it is too low. An analogy would be hyperthyroid and hypothyroid states. Just as hyperthyroidism is treated with medications that suppress the expression of thyroid hormone, high-dose naltrexone might be used to ameliorate symptoms of autism. Just as low thyroid function is treated with exogenous hormonal replacement, fibromyalgia would have to be treated with an intervention that increases endogenous opioid tone. Unlike the situation with the peripheral thyroid gland, the expression of endogenous opioid hormones by the brain means that there are intersecting checks and balances against too much opioid tone.

This is where the concept of intense brain regulation of endogenous opioid tone can be used to design an effective treatment. Exogenous opioids would be hypothesized to be helpful in the short term, but they would worsen the disease in the long term by inducing the "b" process of drivers of pain, anxiety, depression, and separation-distress. Ramanathan, Panksepp, and Johnson (2012) showed the efficacy of low-dose naltrexone for fibromyalgia over a six-month course of treatment. A transient blockade of opioid receptors is hypothesized to induce a rebound of endorphin tone (Brown & Panksepp, 2009) by opponent process. For addicted patients, low-dose naltrexone was used to induce a return to normal endogenous morphine tone after suppression by exogenous hormone. So treatment of fibromyalgia and of opioid dependence would both involve the use of low-dose naltrexone to restore normal endogenous opioid tone. Naltrexone administration would have to be permanent for fibromyalgia because the tissues involved in endogenous opioid tone have been damaged by an autoimmune diathesis. In contrast, naltrexone administration for opioid dependence is likely to be needed only until exogenous opioid suppression of hormonal function has been reversed.

Two clinical observations are important in a discussion of this innovative treatment. Initially, most patients are intolerant of low-dose naltrexone immediately after detoxification. Patients describe a renewal of opioid-withdrawal symptoms on taking 1/1,000 of the usual dose of naltrexone given for alcohol dependence (0.1 mg). They often report gut cramps, diarrhea, increased pain, sweating, and anxiety. However, if the low-dose naltrexone works optimally, patients then describe and show a very positive state that probably

reflects endorphin rebound, about an hour after taking naltrexone, including a sense of well-being, increased motor activity, social confidence, volubility, and decreased pain. Both blockade and rebound seem to be observable.

Conclusion

Neuropsychoanalytic treatment of opioid dependence may be a modality of treatment that is worth further outcomes-based investigation. Ideally, randomized studies of outcomes of buprenorphine and methadone maintenance for opioid addiction would be compared with this approach, in terms of clinical outcomes as well as possible cost savings. The distinction between the Pain Group and the Addicted Group might be taken into account, since our preliminary results suggest that persons with little psychopathology and only a fear of withdrawal have a different course after detoxification from what appears to us to be real addiction.

We have described a unifying conceptualization of diseases involving alterations in central nervous system opioid tone. Both opioid detoxification and fibromyalgia result in low opioid tone. Everything hurts. Anxiety, depression, and a feeling of social unease are generated by low opioid tone. Inability to use human interactions to increase opioid tone may predispose individuals to taking "a person in a pill." Integrating a physiological and psychodynamic perspective may, therefore, improve treatment outcome, as we have described in this case series. We hope these results encourage further exploration of the hypotheses described herein.

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