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Buprenorphine Treatment of Refractory Depression

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Abstract

Opiates were used to treat major depression until the mid-1950s. The advent of opioids with mixed agonist-antagonist or partial agonist activity, with reduced dependence and abuse liabilities, has made possible the reevaluation of opioids for this indication. This is of potential importance for the population of depressed patients who are unresponsive to or intolerant of conventional antidepressant agents. Ten subjects with treatment-refractory, unipolar, nonpsychotic, major depression were treated with the opioid partial agonist buprenorphine in an open-label study. Three subjects were unable to tolerate more than two doses because of side effects including malaise, nausea, and dysphoria. The remaining seven completed 4 to 6 weeks of treatment and as a group showed clinically striking improvement in both subjective and objective measures of depression. Much of this improvement was observed by the end of 1 week of treatment and persisted throughout the trial. Four subjects achieved complete remission of symptoms by the end of the trial (Hamilton Rating Scale for Depression scores less or equal to 6), two were moderately improved, and one deteriorated. These findings suggest a possible role for buprenorphine in treating refractory depression. (J Clin Psychopharmacol 1994;15:49-57).

Throughout history, opium and its derivatives have had an important role in the pharmacologic treatment of various behavioral disorders and by 1850 were considered to be specific treatments for melancholia. [1] At the turn of the century, the eminent authority Emil Kraepelin recommended tincture of opium for the acute treatment of agitated depression. [2] This use of opium and its derivatives continued to be recommended in psychiatric textbooks until as recently as 1956. [3] However, before the development of modern methods of treatment evaluation, opiate therapy for depression was replaced by somatic treatments such as electroconvulsive therapy and later by monoamine oxidase inhibitors and tricyclic antidepressants. These proved to be effective treatments that lacked the opiates' potential for abuse and physical dependence. Thus, the historically recognized antidepressant properties of opiates have, with a few exceptions, [4-8] received little empirical evaluation.

Currently used antidepressants, all of which act on monoaminergic systems, are neither universally effective nor free from adverse effects of their own. [9] For the benefit of patients unresponsive to or intolerant of these agents, who may constitute 10 to 30% of the population of patients with major depression, [10] alternative drug treatments need to be evaluated. Now, with the development of opioid partial agonist and mixed agonist-antagonist drugs exhibiting much reduced abuse and dependence liabilities, [11] it has become possible to safely evaluate the antidepressant efficacy of opioids.

Among these "second-generation" opioids, buprenorphine has pharmacologic properties that make it particularly attractive as a potential antidepressant drug. Buprenorphine, an oripavine derivative of thebaine, is a partial agonist of the opioid micro receptor with kappa receptor antagonist activity. [12] It has undergone considerable recent clinical investigation as a potential therapeutic agent for drug addiction. [13-15] It is safe even in extreme overdosage, [16] despite being 30 to 40

times more potent than morphine as an analgesic. This lack of toxicity is attributed to its partial agonist action at the micro receptor, which results in a "ceiling effect" on respiratory depression, because it acts primarily as a micro receptor antagonist at high doses. [17] It has a longer duration of action than do conventional opioids, having been studied with alternate-day dosage regimens as a maintenance drug in opiate addicts. [18] The drug has modest mood-elevating effects in humans, which actually decline with increasing dose, and is devoid of the dysphoric effects seen with increasing doses of cyclazocine-like compounds. [17,19] Former heroin addicts report that buprenorphine causes feelings of generalized contentment, but not the "rush" induced by heroin. [20] Even after prolonged administration of high daily doses of the drug, the withdrawal syndrome has been shown to be mild and quite delayed, [17,19,21] although addicts are aware of the absence of the drug almost immediately. [21] One study that found more marked and less delayed withdrawal effects than prior investigations still noted that the peak severity of withdrawal was only 59% of the mean previously reported over the first 10 days after the discontinuation of a significantly lower equivalent dosage of morphine. [22] Furthermore, chronic treatment with buprenorphine has been shown to decrease the self-administration of cocaine in primates [23] and in humans. [24]

Buprenorphine has an electroencephalographic profile in the rat similar to that of cyclazocine, [25] an opioid mixed agonist-antagonist with micro antagonist and kappa agonist properties. Cyclazocine was studied as an antidepressant because it's encephalographic profile was similar to that of imipramine. [26] It was shown in that study to have antidepressant properties in both acute and chronic depression in a mixed psychiatric population. However, it is not clear that cyclazocine has clinical properties that can be equated with buprenorphine, because the drugs have opposite activities at the micro and kappa receptors and because cyclazocine does not share its imipramine-like electroencephalographic profile with buprenorphine in humans. [21] In any case, the utility of cyclazocine came into question when it was found to have psychotomimetic properties, [27] a feature that buprenorphine does not have, and it was removed from clinical use.

Motivated by recent evidence that buprenorphine appeared to be safer clinically than conventional opiates, as well by a historical literature describing the antidepressant efficacy of opiates and more recent investigations of antidepressant properties of endogenous opiates, Emrich and colleagues [2] undertook the first published study of buprenorphine as an antidepressant. This double-blind, placebo-controlled study used an A_1 -B-A_2 design and found that there was a robust mean improvement in depressive symptoms over 5 to 8 days of low-dose sublingual buprenorphine administration in a group of 10 depressed patients, most of whom were unresponsive to standard treatments.

Some additional evidence has accumulated subsequently that buprenorphine may have useful antidepressant properties. The drug was associated with reduced depressive symptomatology when substituted for methadone in a population of opiate dependent patients undergoing methadone maintenance. [28] Buprenorphine was also successful in reducing depressive symptoms in patients with borderline personality disorder. [29] Finally, in a placebo-controlled challenge study using 11 non-drug-dependent psychiatric inpatients (8 with depression), buprenorphine induced a marked improvement in mood and behavior in 73% of subjects (and 75% of those with depression); one dysphoric response was observed in a single nondepressed control subject. [30]

This study was conducted to characterize more fully the nature of buprenorphine's potential antidepressant effects, including whether these are persistent beyond the 5- to 8-day period previously studied and whether the drug is effective in treating depression specifically found to be refractory to current standard medication therapies.

Method

Inpatients and outpatients suffering from unipolar major depression without psychotic features that had been unresponsive to adequate trials of antidepressants belonging to at least two different pharmacologic classes (i.e., tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, etc.) were recruited. A minimum Hamilton Rating Scale for Depression (HAM-D) score of 20 and a current episode of at least 3 months' duration were required. Patients who currently met DSM-III-R criteria for psychoactive substance abuse or dependence, had significant medical illnesses, or had undergone electroconvulsive therapy in the previous month were excluded. Potential subjects were told of the possible risks and benefits of treatment with buprenorphine, and if they chose to be considered for the trial, they read and signed an informed consent.

Potential subjects underwent a comprehensive psychiatric evaluation, which included a review of all available records, a physical examination, a standard battery of clinical laboratory studies, and a diagnostic psychiatric interview. If study criteria were met, baseline psychopathology scales were administered. These included the 21-item HAM-D, [31] the Atypical Depression Diagnostic Scale (ADDS), [32] the Profile of Mood States (POMS), [33] and the Global Assessment Scale (GAS). Patients were then taken off of all psychotropic medications other than previously established benzodiazepines (in four subjects, and in one patient, long-established pemoline). Buprenorphine was initiated at 0.15 mg every morning, intranasally [3] or sublingually. [2] We used the preparation of buprenorphine hydrochloride solution currently marketed in the United States for parenteral administration. This comes in small ampules containing 0.3 mg of the drug in 1 ml of aqueous solution. Dosage was titrated according to tolerance and clinical benefit, with a maximum daily dosage of 1.8 mg. Repeat assessments were performed at the end of each week of buprenorphine treatment, including each scale that had been administered at baseline. Laboratory studies and physical examination were repeated after 4 weeks of treatment. Changes in scale scores were analyzed for statistical significance by the use of paired t-tests. For all measures, $p < 0.05$ was considered significant.

Results

Ten subjects (five inpatients and five outpatients) met criteria for inclusion, but three were unable to tolerate the drug and dropped out after one or two doses because of nausea, malaise, or dysphoria. Three subjects completed 4 weeks, and four completed 6 weeks. Of the three who dropped out after 4 weeks, one did so because of persistent nausea, one because of sedation, and one as a result of personal crisis. Of those completing at least 4 weeks, four were men, three were inpatients, and the mean age was 44 (range, 24 to 70). All subjects met DSM-III-R criteria for recurrent major depression without psychotic features, with a mean age at the time of onset of 23.3 years (standard deviation [SD] = 8.8) and a duration of illness of 20.7 years (SD = 11.1). Concurrent DSM-III-R axis I diagnoses included Dysthymic Disorder (all subjects), Somatoform Pain Disorder (N = 2), Opioid Dependence in remission (N = 1), Psychoactive Substance Abuse not otherwise specified in remission (N = 2), Alcohol Dependence, in remission (N = 2), Posttraumatic Stress Disorder (N = 1), and Social Phobia (N = 1). The mean number of antidepressants previously tried was 7.6 (SD = 5.7). By the ADDS, [32] three subjects, including the single nonresponder, met criteria for definite atypical depression (greater or equal to 50% mood reactivity plus two associated features, which may include hypersomnia, leaden paralysis, hyperphagia, and rejection sensitivity), two met criteria for probable atypical depression, (greater or equal to 50% mood reactivity, and one associated feature), one met criteria for simple mood reactive depression (greater or equal to 50% mood reactivity without associated features), and one did not meet criteria for atypical depression or reactivity of mood. The mean baseline HAM-D score was 28.1 (SD = 6.6), and the GAS score was 40.1 (SD = 9.0).

Results for subjects completing at least 4 weeks of treatment are displayed in Table 1. Six of seven subjects achieved marked clinical improvement by the end of the trial, and one deteriorated. The final buprenorphine dosage averaged 1.26 mg/day (SD = 0.55). The mean endpoint HAM-D score was 10.7 (SD = 9.3), representing a 60.7% reduction from baseline ($p = 0.006$), and the GAS score was 58.3 (SD = 19.0), a 45.4% increase from baseline ($p = 0.01$). Approximately 50% improvement was seen in subjective indices of depression (POMS subscales reflecting depressed mood states) at the endpoint. Statistically significant improvement in the mean values of all

parameters became evident at the end of 1 week of treatment, and there were no statistically significant differences between ratings at the end of 1 week and at the completion of the trial. It is notable, however, that at the endpoint, four subjects (57.1%) had HAM-D scores of six or less, whereas at 1 week, only one subject had improved to that extent. To provide more clinical information about the effects of buprenorphine on patients with treatment-refractory depression, we provide detailed vignettes on four selected responders (patients 1 to 4) and the one nonresponder (patient 5).

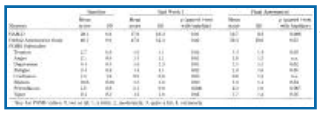

Table 1. Comparison of clinical measures pretreatment, at 1 week, and at the conclusion of the buprenorphine trial in seven subjects completing 4 to 6 weeks of treatment.

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Case Reports

Patient 1

This outpatient was a 45-year-old, married, white academic physician with lifelong dysthymia, in psychotherapy since his late 20s for the treatment of chronically depressed mood, low energy, social anxiety, and pervasive pessimism. In residency training, he had extensive dental work and was treated with oxycodone and acetaminophen. This raised his energy and his mood and relieved his social anxiety. He subsequently took opiates whenever he had the opportunity, moving over time to intravenous use. On several occasions, he became mildly dependent and suffered withdrawal symptoms and a return of depression when his supply ran out. For the first several weeks of an episode of opiate use, his work performance was markedly improved, as was his enjoyment of social interactions. He would then become tolerant, requiring higher doses to achieve less effect. He obtained opiates at work and never interacted with the illicit drug scene. He was finally discovered at work with a supply of hydromorphone and was forced to enter outpatient drug abuse treatment. His depressive symptoms immediately recurred, and his psychiatrist started him on amitriptyline, which was continued at 150 mg/day for over 5 years. This improved his sleep and reduced some of the somatic manifestations that he associated with depression, especially an epigastric sensation of butterflies. However, he continued to suffer from low energy, easy fatigue, social anxiety, a pessimistic outlook, and little enjoyment in life. In addition to receiving medication, he was in intensive psychotherapy and group therapy with a renowned expert in the treatment of addictions and in Narcotics Anonymous. His career and personal life moved ahead, but he gradually got discouraged that he would ever be happy in an abstinent state. After 5 years, he again began to abuse opiates intravenously. He again experienced a marked enhancement of his quality of life. Over a 6-month period, he got married, acquired a new home, and made strides in his research. He was then discovered by the hospital to be using opiates and was induced to undergo inpatient drug abuse treatment and give up his medical license. Again, he relapsed into depression. A course of amoxapine gave him some relief, but this disappeared after a few months. Subsequent trials of phenelzine, bupropion, and fluoxetine were without effect, and he was returned to amitriptyline. He began to have suicidal thoughts. He withdrew from research activities and rarely left home. At this point, he was referred for a trial of buprenorphine on an outpatient basis.

On initial assessment, he had a HAM-D score of 30, with prominent anxiety with diurnal variation, obvious retardation, very depressed mood, profound lethargy, and frequent middle awakenings. His affect was downcast and flat, and he made almost no eye-contact. Because of partial mood reactivity and leaden paralysis, he had criteria for probable atypical depression.

Amitriptyline was discontinued, and buprenorphine was rapidly titrated to 0.15 mg intranasally thrice daily. At the end of a week, he was feeling noticeably better, with more energy and less anxiety. His HAM-D score dropped to 20. By the end of the second week on the same dose, his HAM-D score was down to 17, with markedly reduced retardation, good sleep, and a new hope for the future. His dosage was pushed slightly to a total of 0.6 mg/day for the third week, and his HAM-D score dropped to 14. He remained at this dosage for the remainder of the 6-week study, by which time, his HAM-D score had dropped to eight. By that time, he had returned to his research and writing. Over the next few months, his dosage was raised to 0.3 mg thrice daily and 0.45 mg at bedtime intranasally, to maximize his subjective benefit. At this dosage, he felt he had not only recovered from depression, but had achieved a new level of well-being and hopefulness. He reported much more subtle subjective effects of buprenorphine compared with his prior experience with opiates and particularly noted both a lack of acute euphoria and an absence of tolerance to the mood-elevating effects over time.

He has remained on his present dose for over 2 years. At his wife's request, he has occasional, random, urine toxic screens and has never had metabolites of any other drug in his urine. He is developing a new career in marketing research and has taken up writing, an old ambition he has finally decided to pursue. The combination of high legal expenses and understandably unpleasant memories has discouraged him from attempting to regain his medical license.

Patient 2

This inpatient was a 41-year-old, married, white, male, high-level computer programmer with two young children. A very religious man, he was quite involved in his church and a politically active conservative. His first episode of depression was at age 15, when he left school for a semester, although he was not treated. Since that time, he never felt completely recovered for more than a few months at a time, and these intervals were years apart. The rest of the time he was, to varying degrees, depressed. His last long period of euthymia had come 14 years earlier, when he was married, but it lasted only 6 months.

His depression was characterized by lethargy, slowed thinking, impaired concentration, malaise, hypersomnia (sleeping up to 14 hours/day), and overeating, especially carbohydrates. He weighed 319 pounds. He was not particularly troubled by anxiety and never had psychotic symptoms. He had never had any periods of elevated mood. He had no history of alcohol or substance abuse, nor any experience with medically prescribed opiates.

The patient had been treated initially with desipramine, which as partially effective for several years but then lost efficacy. An amoxapine trial failed. The patient experienced partial improvement for 6 months on fluoxetine, but then relapsed. A trial of bupropion was then begun and seemed to help somewhat for about 3 months, followed by another relapse and another trial of fluoxetine at 80 mg. Throughout this trial, he steadily deteriorated, to the point of requiring hospitalization for the first time. A trial of monoamine oxamine inhibitors was suggested, but during the long fluoxetine washout period, he was referred for an inpatient trial of buprenorphine.

On initial evaluation, he was tearful and markedly psychomotor retarded and reported 5 months of the worst depression of his life. He complained of lethargy and complete inability to function at work or at home and admitted to a strong suicidal drive. Hypersomnia and hyperphagia were not marked, so he was rated only as having probably atypical depression, with a HAM-D score of 21.

He had a very rapid response to buprenorphine, feeling markedly better after his first intranasal dose of 0.15 mg, and at the end of a week of 0.15 mg thrice daily, he reported himself to be 90% recovered. His HAM-D score was down to four; he awoke at 6:30 in the morning feeling refreshed and was no longer lethargic. His demeanor changed completely; he conversed spontaneously, with a full range of affect, and he spoke and moved at a normal pace. By the end of 2 weeks, he felt completely recovered, was discharged from the hospital, and returned to work a week later. For the rest of the 6-week trial his HAM-D score was between three and six. His dosage regimen remained at 0.15 mg thrice daily. He reported a consistent but subtle decline in mood in the morning before his first dose of the day, although he did not feel any subjective "high" or any subjectively apparent drug effect other than a normalization of mood exceeding that induced by any previous antidepressant. His work performance was fully back to normal, and his ability to focus on computer programming was somewhat enhanced. He was involved in church activities with more enjoyment and energy than in the past. He also noticed the disappearance of his carbohydrate craving, and by the end of 10 weeks, he had lost 19 pounds, although he was eating a normal diet. Having elected to continue on the drug, at that time, his HAM-D score was seven. Arrangements were made for him to be given buprenorphine by his health maintenance organization (HMO) physician. Soon thereafter, he missed a follow-up appointment, did not return phone calls, and was lost to follow-up for almost 2 years, when we received a phone call from his HMO internist. He reported that, to maintain the patients remission, repeated dosage increases had been required at several-month intervals, and he wanted to know if an increase from 3 to 3.3 mg/day intranasally would be safe. He was reassured to learn that heroin addicts were routinely treated with much larger doses. There has been no subsequent contact in the year since.

Patient 3

This outpatient was a 28-year-old, single, white man with a history of chronic fluctuating depression since age 12. His childhood adjustment was suggestive of attention deficit disorder without hyperactivity. His early home life was turbulent. He completed high school and a single semester of college before dropping out. He had held a variety of jobs, sometimes working for his father's firm and at other times in unskilled jobs. He rarely held a job for long because he would soon develop tensions and conflicts with employers and quit or be fired. He was referred into the study from an outpatient psychiatric rehabilitation program where he had been engaged in sheltered employment for over a year.

His psychiatric symptoms included baseline depressed mood, chronic lethargy, hypersomnia with intense anxiety with intermittent panic attacks, and multiple forms of idiopathic pain. For back and neck pain and headache, he occasionally received narcotic pain medication, which he stated made him feel more sociable, lively, and "normal."

He was in psychotherapy almost continuously after age 17. His depressive symptoms failed to respond to trials of doxepin, trazodone, phenelzine, and lithium. The patient claimed that nomifensine was very effective, but it was taken off the market. Carbamazepine was judged to be helpful by his psychiatrist, but the patient noted no benefit. Alprazolam was markedly effective for his chronic anxiety, but he abused it. He did not abuse clonazepam, which reduced his chronic anxiety and panic attacks, but left him depressed and anergic. A trial of bupropion increased his anxiety, at which point, he agreed to participate in the buprenorphine study.

At the beginning of the trial, his HAM-D score was 32. He could talk only about his depression, was conspicuously anxious, complained of various pains and deep lethargy, and described significant recent weight loss and diurnal variation of mood. Because he reported almost total anhedonia, he did not meet criteria for any degree of atypical depression. He gave the impression that he was exaggerating the severity of his distress to some extent, although he was obviously quite ill. His only concurrent psychotropic medication was clonazepam (5 mg/day in divided doses). He was not taking any medications for pain.

By the end of 1 week, on a total daily dose of 0.6 mg of buprenorphine, he reported dramatic improvement in mood. His HAM-D score dropped to 10, his anxiety was much diminished, his various pains persisted but were noticeably reduced, and he reported more energy and renewed vitality. He was beginning to get back in touch with neglected friends. He felt his capacity for pleasure was returning. He did complain of an end-of-dose effect, about 4 hours after administration, with a noticeable increase in his familiar symptoms. To overcome this, his dosage was increased in stepwise fashion over the next 5 weeks to 0.6 mg thrice daily, given sublingually. This strategy was effective, and his mood and function continued to improve, so that at the end of 6 weeks, his HAM-D score had dropped to six. He did have several exacerbations of neck pain over the course of the trial and was treated by a rheumatologist with local lidocaine injections and oral doses of oxycodone with acetaminophen, which he reported had less effect than usual on his pain and no effect on his mood.

He elected to continue on buprenorphine after the end of 6 weeks, reporting that he felt better than he had in years. He remained on the sublingual, 0.6-mg, thrice-daily dose over the ensuing 6 months, during which he reported feeling well. Then, attempts by his outpatient rehabilitation program to mobilize him back to full employment appeared to result in a return of physical complaints and anxiety. His father became quite angry at this and markedly reduced his financial assistance to the patient.

Rapidly deteriorating now, the patient was unable to get out of his apartment to refill his prescription for buprenorphine, and he went 48 hours without the drug. He called to report acute withdrawal symptoms, with insomnia, anxiety, nausea, gooseflesh, arthralgias, and malaise. This improved 24 hours after the resumption of buprenorphine, and he concluded that he was dependent on the drug and wanted to be taken off of it. At this time, his HAM-D score had risen to 20. He was placed on a 5-week taper and was monitored closely. At his request, he was simultaneously placed on fluoxetine, an antidepressant he had never tried. Throughout the taper, he complained of fluctuating withdrawal symptoms, now including sweating, trembling, diarrhea, abdominal cramping, and "drug craving," but he had normal vital signs and no physical evidence of diaphoresis or tremor on repeated examination. His complaints of withdrawal symptoms persisted for a month after the discontinuation of the drug. He reported a full depressive relapse.

Patient 4

This inpatient was a married, 70-year-old, white woman with a 39-year history of recurrent major depression with typical melancholic features. In the years before this hospitalization, she had failed to show significant benefit from trials of 19 different antidepressant drugs in various combinations, including an innovative trial of methadone, as well as several courses of electroconvulsive therapy, both unilateral and bilateral, totaling 75 treatments. Before the onset of a postpartum depression at 31, she denied any history of psychiatric illness, and she had functioned well as a mother and homemaker. Since her first depressive episode, she had required many hospitalizations for severe depressive exacerbations and had made three serious suicide attempts. During interepisode intervals in the past, she had enjoyed a significant degree of improvement and had been able to assist her husband in running a small jewelry store. Since their retirement 12 years before the current hospitalization, she reported constant depression of fluctuating severity. She had no history of mania or hypomania and had never abused alcohol or drugs. Her mother had also suffered from recurrent major depression, although less severe.

The present episode had begun 2 years before she entered the study, with mounting symptoms of restless anxiety, and had progressed to include global insomnia, marked diurnal variation of mood with morning worsening, loss of appetite with a 20-pound weight loss over 6 months, pervasive hopelessness, and finally, persistent suicidal ideation, which had resulted in her rehospitalization. Because of her discouraging history of medication nonresponse, she was hospitalized on a cognitive-behavior

treatment unit in the hope that she might find some benefit from cognitive-behavioral treatments. Because of the severity of her current depression, she was found to be unable to participate in cognitive-behavior therapy, and she was referred for experimental treatment with buprenorphine.

Her baseline HAM-D score was 39. She reported 100% maximum reactivity of mood and therefore was categorized as having simple mood-reactive depression. She lacked all other features of atypical depression. She tolerated a steady titration of buprenorphine administered sublingually to 1.8 mg/day over 6 weeks. Within 4 days of initiating the drug, she became capable of enough interpersonal interaction to participate to a limited extent in inpatient cognitive-behavior therapy, although after 1 week, her HAM-D score was still 35. Her improvement was more gradual than that of other responders. After 5 weeks, her HAM-D score had dropped to 22, and she was released from the hospital. One week after returning home, at the end of the buprenorphine trial, her HAM-D score was 11. By this time, she had returned to her former leisure activities of bridge and dining out with her husband and her friends. She elected to remain on the drug, feeling better than she had in many years. She continued to enjoy this remarkable improvement for 8 weeks, when she was dismayed to find herself slipping into a terribly familiar depressive state with no apparent precipitant. Her buprenorphine dosage was systematically increased every few days up to a total of 3.6 mg/day, with no benefit. The dug was then tapered over 2 weeks, and she was monitored closely for 10 days after discontinuation. The patient reported mild nausea and myalgias, but minimized the significance of these, and did not feel her depression was worsening as buprenorphine was withdrawn.

Patient 5

This inpatient was a 33-year-old, single, white man who reported unremitting depression since childhood. He could recall no periods of happiness, only varying degrees of distress. At age 10, he tried to hang himself, in the context of an exceptionally brutal and chaotic family environment. He ran away from home in early adolescence and supported himself by prostitution for several years. During this period, he began to practice self-mutilation by cutting his wrists superficially at times of increased distress; this behavior had continued up to the present. He had also abused multiple drugs including cocaine, marijuana, hallucinogens, and phencyclidine. He gave these up in favor of heavy alcohol abuse in his early 20s and now reported being sober for the past 8 years.

He had worked at several unskilled jobs until disabled by a back injury 4 years ago. He was first hospitalized at that time, at age 29, after a suicide attempt that appeared to have been caused by worsening depression and pain resulting from his back injury. There had been three subsequent hospitalizations for similar reasons. He had been treated with multiple tricyclic antidepressants, fluoxetine, several neuroleptics, lithium, and carbamazepine-all with minimal effects. Monoamine oxidase inhibitors were quickly abandoned because of his expressed fantasy about how easy suicide would be with these. Several psychostimulants were tried, with improvement in energy, concentration, and alertness, but they failed to change his mood. He required opioids intermittently since his back injury; two attempts to treat it surgically had been unsuccessful. He found his mood and general level of function to be elevated by these prescribed opioids, especially oxycodone.

On initial assessment, he was receiving perphenazine, 12 mg, magnesium pemoline, 37.5 mg, and codeine and acetaminophen as needed for back pain. He was eager to try buprenorphine and agreed to discontinue perphenazine, which had no clear indication. He insisted on continuing pemoline, which had been at a constant dose for 2 years, with good effect on his energy level and alertness. He had a 21-item HAM-D score of 26, with long initial insomnia, feelings of guilt, frequent spasms of anxiety verging on panic attacks, and somatic symptoms of pain and anergia. He had no psychomotor retardation and was without any evidence of delusions or thought disorder. He reported 80% mood reactivity, severe leaden paralysis, ravenous appetite, and extreme sensitivity to rejection and therefore met criteria for definite atypical depression.

He had a dramatic initial response to buprenorphine, at the end 1 week feeling more alert and more relaxed than in many years. His HAM-D score dropped to 11. He was much more sociable, and his initial insomnia resolved without daytime sedation. His back pain was reduced, and he dropped his use of as-needed codeine by two-thirds. He complained only of mild nausea. However, a week later, he was doing less well, despite increases in dosage to 0.6 mg/day. His pain was worse, his nausea had intensified, and he developed early morning awakening with guilty ruminations; his HAM-D score was now 20. Over the subsequent 2 weeks, his condition deteriorated further. This followed his longtime therapist's revealing his decision to terminate psychotherapy with the patient, after several years of acting as his primary social support. In an effort to recapture his initial benefit, the buprenorphine dosage was increased in stepwise fashion to 0.6 mg intranasally three times a day. His nausea subsided, and he denied any subjective awareness of buprenorphine, but he continued to feel worse, with a dramatic increase in back pain and feelings of rage and betrayal. He exhibited frequent, intense hostility and uncooperativeness toward hospital staff. He abruptly decided that no medication could help him and refused to participate further in the study. His HAM-D score on his final interview, after 4 weeks on the drug, was 30. He developed no withdrawal symptoms over the subsequent several weeks, although he complained of severe headaches.

Discussion

The degree of benefit experienced by this treatment-refractory group of depressed patients is striking. The large number of previous treatment failures experienced by these subjects and the severity of their index episodes would argue against this being a placebo response in most cases, especially given the relatively extended period of improvement observed. [35] Placebo response is rare in this population, recently estimated to be approximately 10%. [36]

The rapidity of onset of clinical improvement replicates that observed in prior studies. [2,26,30] The pattern of slow, steady improvement customarily seen with antidepressant therapy was not observed, with most improvement noted within 1 week.

Patients did not feel intoxicated or euphoric, but rather, "more normal," as several remarked. The POMS contains euphoria scales that are likely to become quite elevated when the patients are in intoxicated states. [37] Although these three scales (elation, friendliness, and vigor) were significantly elevated from baseline, they rose to only modest absolute scores (as shown in Table 1). Of course, this may simply indicate that depressed subjects are not capable of a full euphoric drug response. It is notable that, for one-third of the subjects, the effect of the drug was subjectively so unpleasant that they withdrew after one or two doses, a finding that suggests that buprenorphine does not have a high abuse potential in this population. This is even more striking if one considers that another third of the subjects chose to withdraw after 4 weeks of treatment, despite having experienced some antidepressant benefit.

It is also worth noting that the dosage of buprenorphine used in this protocol was quite low, in keeping with prior published experience in this population. [2,30] The average final dose used during the trial was 1.3 mg/day, whereas in studies of opiate abusers, buprenorphine dosages begin at 2 mg/day and rise to high as 16 mg/day. [18,38]

Although all but one of these patients met at least threshold criteria for mood reactive, atypical depression, the one patient to deteriorate (in the context of a personal crisis) met criteria for definite atypical depression on the ADDS (patient 5), and the one "typical" (i.e., non-mood reactive) melancholic (patient 3) showed an excellent, although ultimately transient, treatment response, as did patient 4, whose clinical presentation was nearly "typical" of melancholia. Thus, these findings do not argue that the diagnostic subtype of atypical depression predicts treatment response to opioid therapy, although a larger and more heterogeneous population would be

required to make any strong conclusions in this regard.

An intriguing possibility is raised by the marked response to opioid treatment of this group of chronically depressed patients who had been little helped by standard antidepressant drug therapy. Perhaps the pathophysiology of depression in a subgroup of patients is unrelated to abnormalities of central monoaminergic systems, but rather, results from dysfunction of the endogenous opioid system. This might account for the resistance to treatment with standard monoaminergic antidepressants in some patients. It is also consistent with the recent finding that the brains of depressed suicide victims show up to a nine-fold increase in the number of endogenous opioid receptors over age- and sex-matched controls postmortem. This finding suggests that opioid receptor up-regulation may be occurring in this very treatment-refractory population because of a deficit of endogenous opioid neurotransmitter availability. [39]

Our findings are intriguing but tentative. It is striking that, in several cases, clinical benefit did not persist through continuation treatment, raising the suspicion of either tachyphylaxis or a nonspecific placebo effect in some cases. [40] Placebo-controlled studies over more prolonged periods of treatment will be necessary both to rule out a primary placebo effect and to establish the degree to which the antidepressant effects of buprenorphine persist. Fixed-dose designs will be necessary to establish optimal dosing strategies, which were obscured by steady dosage increases over the course of this trial. Comparison with standard agents in treatment-refractory patients will be necessary to establish whether buprenorphine has superior efficacy in treatment-resistant depression, and trials in nonrefractory major depression will be needed to establish whether buprenorphine's efficacy is limited to refractory illness.

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