Reduction of Opioid-Withdrawal Symptoms With Quetiapine

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This article is dedicated to Barbara Ruane.

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Objective: To determine the utility of quetiapine in a population undergoing ambulatory detoxification from opioids.

Method: Medications utilized in our outpatient clinic for opioid withdrawal were evaluated for quality-assurance purposes. The treatment regimen generally included clonidine, hydroxyzine, trazodone, diphenoxylate/atropine, and sometimes chlordiazepoxide. Patients were also initially given eight 25-mg tablets of quetiapine and instructed to take 1 or 2 tablets every 4 hours as needed for symptoms of withdrawal or craving (with a maximum daily dose of 200 mg). Data were based on patient evaluations from June 2003 to June 2004.

Results: 41% of all patients (N = 213) successfully completed the detoxification phase of the program (i.e., completed at least 5 days of abstinence). A medication questionnaire was instituted for quality-assurance purposes after some apparent initial success with quetiapine. A retrospective analysis of these data revealed that, of the 107 patients evaluated for medication response, 79 reported that quetiapine helped reduce craving for opioids, 52 reported that quetiapine helped reduce their anxiety, 24 reported a reduction in somatic pain, 22 reported that quetiapine helped alleviate insomnia, and 14 reported an improved appetite. Four individuals did not feel quetiapine had any benefit, and another 7 were unable to tolerate quetiapine because of side effects. The quetiapine dose used ranged from 25 to 600 mg/day (mean ± SD dose = 206 ± 122 mg/day).

Conclusions: Quetiapine use during opioid cessation was found to help abate symptoms of opioid withdrawal in our patient population and was generally well tolerated.

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Opioid withdrawal is often complicated by physical and emotional stressors, which can lead to relapse during this period. In order to facilitate the withdrawal process, medications are conventionally employed to limit the severity of withdrawal.

Management of withdrawal ideally involves substituting an agent that can be given orally, has a low potential for overdose or abuse, and is relatively free of side effects.[1] Opioid withdrawal is accompanied by flu-like symptoms including muscular aches, dysphoria, insomnia, nausea, diarrhea, and piloerection.[2,3] Withdrawal from heroin can produce symptoms lasting from 7 to 10 days. Withdrawal symptoms from methadone can last 14 days or more.[4] Opioid withdrawal increases central noradrenergic activity, which contributes to the withdrawal symptomatology. This increased activity, in part, is suppressed by clonidine.[5] Long-acting benzodiazepines have been used to further suppress discomfort during opioid withdrawal.[6]

Atypical antipsychotics have also been reported to play a role in facilitating the withdrawal process. In studies of cocaine dependence, symptoms of cocaine withdrawal were reported to be lessened by clozapine[7,8] and quetiapine,[9,10] whereas risperidone[11] and olanzapine[12] did not appear to be beneficial. A literature search revealed no prior reports on the use of quetiapine for patients going through opioid withdrawal.

Quetiapine was initially being used in the inpatient unit at our institution to help control symptoms of opioid withdrawal, and it appeared to have some beneficial effect.

Use of quetiapine was adopted by our ambulatory clinic as a way of minimizing anxiety associated with opioid withdrawal while using a medication with low potential for abuse. In an attempt to systematically investigate the role of quetiapine in this setting, a questionnaire was developed for quality-assurance purposes.

METHOD

Individuals addicted to opioids who presented to the emergency department at Western Psychiatric Institute and Clinic, Pittsburgh, Pa., for treatment of opioid withdrawal were evaluated for comorbid medical or psychiatric problems. Hospitalization was suggested when indicated for medical or psychiatric reasons. Patients not hospitalized were offered an ambulatory detoxification protocol and the option of subsequent psychosocial treatments. Those who accepted were given a 1-day supply of medications to ameliorate withdrawal symptoms (see Results). The patients were referred to follow-up at the ambulatory detoxification clinic the next day. At the clinic, individuals were reevaluated and followed-up on a daily basis. Vital signs were obtained, and patients were interviewed each day. Medications for a 1-day period were prescribed daily. Medication regimens were individually tailored to the patient's withdrawal symptoms. In addition to being given medications, patients were counseled on a daily basis.

Medication regimens were chosen from the following: clonidine, chlordiazepoxide, hydroxyzine, trazodone, and diphenoxylate/atropine. Individuals were also initially given eight 25-mg tablets of quetiapine and instructed to take 1 or 2 tablets every 4 hours as needed for symptoms of withdrawal or craving (with a maximum daily dose of 200 mg). Patients were told that quetiapine is an antipsychotic. The off-label use of quetiapine from its U.S. Food and Drug Administration–approved purpose was explained to each patient, as were the risks for adverse events. Patients were seen again the next day, and medications were refilled on a daily basis. Clonidine was tapered upward as blood pressure permitted; trazodone was adjusted as needed to help with sleep. If the patient tolerated quetiapine and reported a beneficial effect, the patient's maximum daily dose was increased. The reported effect of quetiapine on controlling withdrawal symptoms varied with each patient. The patient's self-report of response to medications was monitored on a daily basis.

A daily questionnaire was initiated after some apparent initial success with quetiapine. Prior to instituting the questionnaire, we consulted our institutional review board (IRB). We were informed that, since the questionnaire was being utilized for quality-assurance purposes, IRB approval was not needed. When using the questionnaire, interviewers attempted to have the patients distinguish the effect of quetiapine from other medications. Patients were also assessed on a daily basis with the Opioid Withdrawal Assessment (OWA) scale.[13] The questionnaires filled out by individuals taking medications for major medical illnesses were not included in this analysis. The questionnaires from those individuals taking antidepressants or anxiolytics at presentation were included in this analysis (see Results). Individuals with comorbid bipolar disorder, schizoaffective disorder, major depressive disorder, or schizophrenia represented a small subset of the total population, and their responses to the questionnaire were not included in the current results. The responses of individuals with a history consistent with anxiety disorder not otherwise specified (NOS) or depressive disorder NOS (predating the onset of opioid abstinence), however, were included in the results. Medication dosages, the average age of subgroups, and the results from the OWA scale are reported as mean values ± standard deviations. The data were based on patient evaluations from June 2003 to June 2004.

RESULTS

Two hundred thirteen patients were treated with the quetiapine regimen in the ambulatory detoxification clinic. The mean OWA scale score for this group on initial presentation to the clinic was 2.1 ± 0.9. Of the 213 patients, 41% completed the program (with at least 5 days of abstinence). Approximately 1 year following the introduction of our detoxification regimen, a quality-assurance protocol was initiated. Only a subcomponent of the initial 213 patients participated in the survey because of the questionnaire's subsequent introduction. The results reported reflect a retrospective analysis of the total data obtained (see Method).

The questionnaires from 107 patients surveyed for quality-assurance purposes were analyzed. Of the 107 patients, 45% did not complete the program (and displayed an initial OWA score of 2.5 ± 1.0 and a final OWA score, prior to dropping out, of 2.2 ± 0.9); 55% completed the protocol (and displayed an initial OWA score of 2.4 ± 0.8 and a final OWA score of 0.9 ± 0.8). The group of patients who left the program prematurely had a mean age of 31 ± 9 years, was 45% male and 55% female, and was 2% African American and 98% white. The group of patients who completed the program had a mean age of 29 ± 11 years, was 61% male and 39% female, and was 9% African American and 91% white. The group that did not complete the program received a maximum daily dose of 0.28 ± 0.15 mg/day of clonidine, 166 ± 96 mg/day of trazodone, 56 ± 54 mg/day of chlordiazepoxide (range, 0 to 150 mg/day), and 221 ± 123 mg/day of quetiapine. The group that completed the program received a maximum daily dose of 0.25 ± 0.15 mg/day of clonidine, 126 ± 98 mg/day of trazodone, 39 ± 46 mg/day of chlordiazepoxide (range, 0 to 175 mg/day), and 189 ± 117 mg/day of quetiapine.

In the group composed of individuals not completing the program, 10% had a comorbid diagnosis of alcohol abuse or dependence, 10% had a comorbid diagnosis of cocaine abuse or dependence, 2% had a comorbid diagnosis of benzodiazepine abuse or dependence, 17% were diagnosed with anxiety disorder NOS, and 22% were diagnosed with depressive disorder NOS. In the group composed of individuals completing the program, 11% had a comorbid diagnosis of alcohol abuse or dependence, 5% had a comorbid diagnosis of cocaine abuse or dependence, 7% had a comorbid diagnosis of benzodiazepine abuse or dependence, 13% were diagnosed with anxiety disorder NOS, and 20% were diagnosed with depressive disorder NOS.

In the group that did not complete the protocol, 2 individuals entered the program taking escitalopram, 1 was taking paroxetine, and 1 was taking sertraline. In the group that completed the protocol, 1 individual entered the program taking mirtazapine, 1 was taking escitalopram, 1 was taking paroxetine, 3 were taking sertraline, 2 were taking bupropion, and 1 was taking buspirone. All of the antidepressants and anxiolytics were initiated prior to the patient seeking detoxification, and the doses at presentation were continued to prevent further complications during withdrawal.

Of the total 107 patients surveyed, 79 (74%) believed that quetiapine helped reduce craving for opioids, 52 (49%) stated that it helped reduce anxiety associated with withdrawal, 24 (22%) reported a reduction in somatic pain, 22 (21%) reported that it helped alleviate insomnia, 14 (13%) noticed an improvement in appetite, 1 stated that it helped reduce gastrointestinal discomfort, and 1 stated that it helped reduce the sensation of piloerection (Table 1). Four individuals found quetiapine to have no effect. Another 7 individuals were unable to tolerate quetiapine because of side effects. The mean ± SD maximum quetiapine dose given to each of the 107 patients was 206 ± 122 mg/day.

Table 1. Effect of Quetiapine on Opioid Withdrawal (N = 107)

Effect	N (%)
Reduced craving for opioids	79 (74)
Reduced somatic pain	24 (22)
Reduced anxiety	52 (49)
Helped alleviate insomnia	22 (21)
Improved appetite	14 (13)
Reduced gastrointestinal discomfort	1 (1)
Reduced sensation of "gooseflesh" (piloerection)	1 (1)
Reduced "twitching"	1 (1)
Unable to tolerate side effects	7 (7)
None	4 (4)

DISCUSSION

There is little published information on the role of antipsychotics in treating opioid withdrawal in the nonpsychotic population. Preliminary work on small patient populations suggested that the typical antipsychotics reduced opioid withdrawal symptomatology.[14] Quetiapine has been reported to be beneficial in reducing cannabis use in patients with comorbid psychosis[15] and craving for cocaine in patients with comorbid psychopathology.[9,10] A review of atypical antipsychotic use in drug-addicted patients with schizophrenia[16] theorized that clozapine, quetiapine, and olanzapine may be beneficial in the treatment of comorbid substance abuse. Several possible modes of action were proposed including an effect of these drugs on the reward system.[15,16] The present study made no attempt to compare various antipsychotics, and it is possible that some of the other atypical antipsychotics may be beneficial. Quetiapine was initially chosen for the outpatient clinic because of its sedating effects, with the hope that it may supplant the use of benzodiazepines. There were, however, several individuals requiring chlordiazepoxide in addition to quetiapine for the treatment of opioid withdrawal. In addition, several individuals were also being treated with chlordiazepoxide for comorbid alcohol or benzodiazepine withdrawal.

Chlordiazepoxide dosing was carefully monitored because of the potential for abuse and diversion. Patients were given a 1-day supply of chlordiazepoxide at a time, and an attempt was made to rapidly taper the dose. Patients were monitored for possible signs of abuse on a daily basis.

In the setting of an ambulatory detoxification clinic, quetiapine appears to play a role in helping to abate opioid withdrawal symptoms. Doses of up to 600 mg/day of quetiapine were generally well tolerated (prescribed using p.r.n. dosing) with a fairly rapid upward titration. Quetiapine dosing was increased if the individual felt a beneficial response, although the beneficial effects that were reported varied. Seventy-four percent of the patients surveyed experienced a reduction in opioid craving with quetiapine, and 49% experienced a reduction in anxiety. Some patients reported that quetiapine specifically made a large difference in their ability to tolerate the withdrawal protocol. A minority of patients requested to be continued on quetiapine following the detoxification process. Some individuals reported a fear of relapsing and felt quetiapine helped maintain abstinence. In those cases, quetiapine dosing was continued for approximately 5 days before being discontinued. All individuals were offered follow-up therapy as well as medication management after they completed the program.

This evaluation was subject to bias as there was no control population and the treatment was open label. Nevertheless, it appears that quetiapine may play a role in opioid detoxification, although the pharmacologic mode of action is not known. The results of this analysis suggest the need for further investigation.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), chlordiazepoxide (Librium and others), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, FazaClo, and others), diphenoxylate/atropine (Lomotil, Lonox, and others), escitalopram (Lexapro), hydroxyzine (Vistaril, Atarax, and others), methadone (Methadose, Dolophine, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others).

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