Double-Blind Treatment With Oral Morphine in Treatment-Resistant Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) often responds inadequately to serotonin reuptake inhibitors (SRIs). A case series reported substantial response to once-weekly oral morphine. We conducted a placebo-controlled, double-blind trial to investigate whether once-weekly oral morphine is effective in SRI-resistant OCD.

Method: Subjects with DSM-IV–defined OCD for ≥ 3 years who had failed ≥ 2 adequate SRI trials and had a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score of ≥ 20 were recruited. Current medications were continued. Subjects were randomly assigned to random-order, 2-week blocks of once-weekly morphine, lorazepam, and placebo. Week 2 dosage was increased, decreased, or maintained depending on response and side effects.

Results: We enrolled 23 subjects, who had failed 2 to 6 SRI trials. The median screening Y-BOCS score was 29. The median Y-BOCS score after morphine (highest dose) was 25 (median decrease = 13%). Seven subjects (30%) were responders (Y-BOCS decreases ≥ 25%). The median Y-BOCS score after lorazepam (highest dose) was 27 (median decrease = 6%). Four subjects (17%) responded to lorazepam; 1 was a morphine responder. The median Y-BOCS score after placebo (highest dose) was 27 (median decrease = 7%), and no subject responded. Responses differed significantly among the 3 conditions (Friedman 2-way analysis of variance, $\chi_r^2 = 13.92$, df = 2, p = .01). Wilcoxon matched-pairs signed-rank tests (T = 56.5, p = .05) showed significance for morphine versus placebo but not lorazepam versus placebo.

Conclusion: Our results support the hypothesis that once-weekly oral morphine can reduce symptoms in some treatment-resistant OCD patients. The mechanism of action is unknown. Further studies of mu-agonists and glutamate antagonists are warranted.

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Serotonin reuptake inhibitors (SRIs) are the only U.S. Food and Drug Administration–approved medications for the treatment of obsessive-compulsive disorder (OCD). However, 20% to 40% of OCD patients fail to respond satisfactorily after 2 or more adequate SRI trials.[1] With the lifetime prevalence of OCD standing at 2% to 3%,[1] this poor response translates into significant morbidity and dysfunction for millions of U.S. adults. Furthermore, the maximum response of OCD to approved drugs is usually only partial, is delayed 12 weeks or more, and is accompanied by significant side effects.[2] Treatment resistance, partial response, and the side effect profile of medications approved for OCD treatment create the need for studies of new treatment approaches.

A case series[3] and an open-label trial[4] suggest a role for mu-opioid receptor agonists in the management of treatment-resistant OCD. Of interest is the high concentration of opioid receptors in the striatal system, particularly the caudate nucleus, an area that appears important in the pathophysiology of OCD.[5] Warneke[3] reported 5 cases of severe, treatment-refractory OCD that responded to oral morphine sulfate, 20 to 40 mg, given every 5 to 8 days. The therapeutic response was not accompanied by euphoria or medication-seeking behavior. One morphine responder had undergone 2 unsuccessful neurosurgical interventions (bilateral cingulotomy and bilateral anterior capsulotomy).

Shapira et al.[4] conducted a 6-week open-label study of the mu-receptor agonist tramadol (mean dose = 254 mg/day) in treatment-refractory OCD. Tramadol has lower abuse and dependency liability than morphine. In vitro studies indicate that tramadol's mu-opioid receptor af-

finity is 6000-fold less than morphine's. Tramadol also exhibits modest serotonin and norepinephrine reuptake inhibition. Of the 7 patients enrolled in the study, 1 dropped out at week 1 because of nausea and worsening trichotillomania. Intent-to-treat analysis for the 6 patients who completed at least 2 weeks of the treatment showed a Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[6] mean score decrease of 26%; 3 patients responded within 1 week of starting treatment with the drug.[4] Two additional cases responding to tramadol have been reported, 1 within 24 hours,[7] 1 after an indeterminate period.[8]

To investigate further the possible role of mu-opioid receptor agonists in the management of OCD, we conducted the first placebo-controlled, double-blind trial testing the hypothesis that once-weekly oral morphine is effective in the management of treatment-resistant OCD.

METHOD

Patients

Between February 2000 and October 2003, we recruited subjects aged 18 to 60 years with DSM-IV–defined OCD for ≥ 3 years who had failed 2 or more adequate SRI trials and had Y-BOCS scores ≥ 20. An "adequate" SRI trial was defined as ≥ 8 weeks at a dose found effective for OCD in controlled trials. Concurrent psychotropic medications were continued with doses unchanged, but doses at study entry must have been stable for at least 2 months. Eligible subjects had no unstable medical illness and no relative contraindication to opiate administration, including no chronic obstructive pulmonary disease, chronic constipation, or cardiovascular compromise. Eligible subjects also had no history of substance or prescription medication abuse, psychosis, mania, or antisocial personality disorder. Concurrent OCD-focused behavioral therapy was not allowed. Diagnoses were established using the Mini-International Neuropsychiatric Interview (MINI).[9] After the study was fully explained, all subjects signed an informed consent statement approved by the Stanford University Medical Center institutional review board.

Study Design

Subjects were enrolled for 7 weeks. One week after the screening visit, subjects began study medication in randomly ordered, 2-week blocks of once-weekly oral morphine sulfate, beginning at 30 mg; lorazepam, beginning at 1 mg; and placebo. Week 2 dosage in each drug condition was increased, decreased, or maintained unchanged depending on response and side effects. For morphine, the week 2 dose ranged from 15 to 45 mg; for lorazepam, 0.5 to 2 mg. Because of the short half-life of study drugs, no washout period was interposed between the 2-week blocks. All medications were administered in the clinic. Subjects were observed on site for 2 hours after each administration to guard against respiratory depression. The research assistant monitoring the subject noted spontaneously reported side effects.

Assessments

The screening visit included administration of the MINI, medical and psychiatric history-taking, and drawing blood for standard laboratory tests. In addition, the Y-BOCS[6] and the Montgomery-Asberg Depression Rating Scale (MADRS)[10] were administered to measure OCD and depressive symptoms, respectively. The Y-BOCS and MADRS were also administered at the baseline visit (end of week 1, at which time subjects received the first dose of the first medication) and at the end of weeks 2, 3, 4, 5, 6, and 7. At each visit, the research assistant noted subject-reported side effects for the week between visits. Response was defined a priori as a ≥ 25% decrease from screening visit Y-BOCS score after the highest medication dose attained. (When medication doses were the same at both visits but the Y-BOCS score was different, the Y-BOCS score for the second visit was used in the analyses.)

All ratings were performed by psychiatrists blinded to the subjects' medication side effects. In addition, the rating psychiatrists remained blinded to the morphine/lorazepam/placebo response of all study subjects until the entire study was completed. Only the senior author broke the blind with the study subjects at the end of their participation and then arranged for follow-up care with physicians not participating in the study.

Statistical Analysis

Because the subjects' rating scale scores were not normally distributed, we utilized nonparametric statistical tests, which do not depend on the assumption of a normal distribution: the Friedman 2-way analysis of variance by ranks, with $p \leq .05$, was used to test whether response differed significantly across drug conditions. The Wilcoxon matched-pairs signed rank test, with $p \leq .05$, was used to test whether drug response differed significantly within subjects. Because the data were not normally distributed, we report them in terms of medians and ranges, but also display mean (SD) changes in Tables 2 and 4 to allow rough comparison to the results of other OCD treatment trials.

To test for the possibility that a morphine response appeared because of a carryover effect from one drug condition to the next, or that the response was related to medication sequencing, a nonparametric Kruskal-Wallis 1-way analysis of variance by ranks was performed using Y-BOCS scores in the first medication period for all subjects, i.e., across the 3 medication conditions. This analysis was followed by the Mann-Whitney U test to determine whether morphine was superior to lorazepam and, separately, to placebo.

Table 1. Concurrent Medications Held at Constant Dose for All Study Medication Conditions[a]

Subject	SSRI	Clomipramine	Benzodiazepine	Gabapentin	Atypicals	Bupropion	Trazodone	Topiramate	None
1									✓
2	✓	✓	✓	✓	✓				
3	✓	✓	✓						
4	✓	✓			✓				
5	✓		✓		✓			✓	
6									✓
7	✓			✓	✓				
8	✓	✓	✓		✓				
9									✓
10	✓		✓		✓				
11									✓
12	✓		✓			✓			
13	✓		✓						
14									✓
15	✓								
16									✓
17[b]			✓	✓					
18[b]	✓			✓		✓			
19[b]						✓			
20[b]	✓								
21[b]	✓		✓	✓			✓		
22[b]	✓		✓		✓				
23[b]	✓								

[a]Total subjects (N [%]) for each medication were as follows: SSRI, 15 (65.2); clomipramine, 4 (17.4); benzodiazepine, 10 (43.5); gabapentin, 5 (21.7); atypicals, 7 (30.4); bupropion, 3 (13.0); trazodone, 1 (4.3); topiramate, 1 (4.3); none, 6 (26.1).
[b]Morphine responder.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

RESULTS

We enrolled 23 subjects, 17 men and 6 women, with a mean (SD) age of 40.0 (7.3) years. Subjects had failed from 2 to 6 (mean = 3.4) adequate SRI trials for OCD, including selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and clomipramine. Eleven subjects, including 1 morphine responder, had failed at least 1 adequate augmentation trial with an atypical antipsychotic drug. Concurrent psychiatric medications included SSRIs (N = 15), benzodiazepines (N = 10), atypical antipsychotics (N = 7), gabapentin (N = 5), clomipramine (N = 4), bupropion (N = 3), topiramate (N = 1), and trazodone (N =1); 6 subjects were taking no concurrent psychiatric medications (Table 1).

The median screening visit Y-BOCS score of the study group (N = 23) was 29 (range, 20–38). The median score after the highest morphine dose was 25 (range, 12–34), and the median difference from screening was –13% (range, +70% to –53%) (Table 2).

The median Y-BOCS score after the highest lorazepam dose was 27 (range, 15–35), and the median decrease was 6% (range, –43% to +14%) (Table 2). In the placebo condition, the median Y-BOCS score after the highest dose was 27, and the median decrease was 7%.

Seven of the 23 subjects were responders to morphine (Y-BOCS score decrease of ≥ 25%). The highest morphine dose was 30 mg for 4 responders and 45 mg for 3. No morphine responder took morphine alone; all were taking concomitant psychotropic medications (Table 1). The only suggestive difference in the concomitant medications of morphine responders versus nonresponders was that, of 7 subjects taking an atypical antipsychotic, only 1 was a responder (Table 1). A subject's OCD symptom distribution did not seem to predict morphine response or nonresponse (Table 3).

Only 1 morphine responder (subject 20, Table 2) also responded to lorazepam, but the morphine response was larger (41% vs. 27%). Three morphine responders were slightly worse after taking lorazepam (Table 2). Four subjects responded to lorazepam; their Y-BOCS score decreases were 43% (vs. 4% for morphine), 29% (vs. 24%), 27% (vs. 41%), and 25% (vs. an increase of 70%). No subject responded during the placebo condition; 1 subject's Y-BOCS score increased 55% (Table 2). The 1 subject (subject 6) with a comorbid tic disorder (Tourette's) did not respond to any drug condition, nor was the severity of his tics affected.

A Friedman 2-way analysis of variance by ranks for percent Y-BOCS score decrease across medication conditions showed that decreases for the 23 subjects differed significantly among the 3 medication conditions (χr^2 =13.92, df = 2, p = .01). The Wilcoxon matched-pairs signed rank test showed significance for morphine versus placebo (T = 56.5, p = .05), but not for morphine versus lorazepam (T = 66.5) or for lorazepam versus placebo (T = 98.5). The Kruskal-Wallis 1-way analysis of variance by ranks of Y-BOCS scores in the first medication period for all subjects showed significant differences (H = 534.9, p ≤ .001) among the groups receiving morphine (N = 7,

Table 2. Y-BOCS Scores and Percent Changes for Each Study Medication Condition

		Morphine		Lorazepam		Placebo	
Subject	Screening Score	Score After Highest Dose	% Difference From Screening	Score After Highest Dose	% Difference From Screening	Score After Highest Dose	% Difference From Screening
1	31	27	–13	29	–6	29	–6
2	25	23	–8	27	+8	28	+12
3	27	24	–11	27	0	24	–11
4	38	29	–24	27	–29	30	–21
5	34	34	0	32	–6	32	–6
6	27	28	+4	23	–15	29	+7
7	23	22	–4	22	–4	24	+4
8	29	33	+14	32	+10	25	–14
9	25	23	–8	22	–12	24	–4
10	30	25	–17	29	–3	28	–7
11	33	29	–12	33	0	32	–3
12	20	34	+70	15	–25	31	+55
13	29	25	–14	25	–14	26	–10
14	28	27	–4	16	–43	26	–7
15	29	30	+3	28	–3	26	–10
16	33	26	–21	25	–24	25	–24
17[a]	21	12	–43	17	–19	16	–24
18[a]	34	20	–41	27	–21	29	–15
19[a]	28	20	–29	29	+4	27	–4
20[a]	22	13	–41	16	–27	20	–9
21[a]	34	16	–53	withdrawn[b]	withdrawn[b]	34	0
22[a]	21	12	–43	24	+14	19	–10
23[a]	33	23	–30	35	+6	32	–3
Median[c]	29.0	25.0	–13	27.0	–6	27.0	–7
Range	20–38	12–34	+70 to –53	15–35	+14 to –43	16–34	+55 to –24
Mean (SD)	28.4 (4.9)	24.1 (6.5)	–14.1 (25.4)	25.5 (5.7)	–9.5 (14.7)	26.8 (4.4)	–5.0 (16.1)

[a]Morphine responder.
[b]Data unavailable due to patient's early withdrawal from the study.
[c]Values for percentage difference from screening have been rounded to the nearest whole percentage.
Abbreviation: Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. Obsessive-Compulsive Disorder Symptom Distributions for Study Subjects at Presentation

	Subject																						
Symptom (N)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17[a]	18[a]	19[a]	20[a]	21[a]	22[a]	23[a]
Mental rituals/counting (14)	✓	✓	✓	✓		✓					✓		✓		✓	✓	✓	✓			✓	✓	✓
Repeating rituals (17)	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓				✓	✓	✓		✓	✓	✓	
Hoarding (10)	✓		✓	✓			✓	✓	✓		✓			✓				✓	✓				
Checking (14)	✓	✓				✓	✓	✓	✓	✓	✓			✓		✓				✓	✓	✓	✓
Religious obsessions (10)	✓	✓	✓				✓			✓			✓		✓						✓	✓	✓
Horrific images (4)		✓					✓								✓	✓							
Aggressive obsessions (10)		✓				✓	✓		✓	✓			✓					✓		✓	✓		✓
Contamination (19)		✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Symmetry (13)	✓		✓	✓		✓		✓	✓	✓			✓	✓		✓				✓	✓	✓	
Need to know (1)				✓																			
Need to touch (1)	✓																						
Somatic obsessions (4)				✓								✓				✓		✓					

[a]Morphine responder.

mean decrease in Y-BOCS score = 14.4%), lorazepam (N = 8, mean decrease in Y-BOCS score = 0.5%), and placebo (N = 8, mean decrease in Y-BOCS score = 6.6%). Mann-Whitney U tests were significant for morphine versus placebo ($U = 6$, $p \leq .01$) and for morphine versus lorazepam ($U = 7$, $p \leq .01$). Therefore, when morphine was the first drug administered, it had a significantly greater effect than did lorazepam or placebo.

The morphine responders described the relief of OCD symptoms as being noticeable the day after taking morphine and lasting from 2 to 5 days. They described decreased frequency and persistence of obsessions, with 2 saying, "my thoughts are clearer." For 2 responders, obsessions decreased from "constant" to 3 to 4 hours per day. All responders reported a decrease in the associated anxiety and an increased ability to resist doing compulsions. All reported that OCD interfered less with their functioning during the morphine condition than at study baseline.

Mean and median MADRS scores at the screening visit were higher among morphine responders than non-

Table 4. MADRS Scores for Each Study Medication Condition

Subject	Screen	Baseline	Morphine	Lorazepam	Placebo
Nonresponders					
1	15	9	8	20	11
2	20	22	20	29	24
3	32	22	27	32	22
4	6	8	7	4	0
5	29	17	17	17	15
6	5	9	11	3	19
7	14	15	18	16	21
8	33	44	45	32	34
9	17	18	10	18	18
10	16	15	20	23	22
11	16	16	14	34	18
12	31	29	38	34	43
13	25	19	27	22	18
14	8	8	7	3	3
15	28	28	15	22	18
16	9	14	3	5	6
Median	16.5	16.5	16.0	21.0	18.0
Mean (SD)	19.0 (9.6)	18.3 (9.4)	17.9 (11.6)	19.6 (11.2)	18.3 (10.7)
Responders					
17[a]	23	20	21	17	16
18[a]	24	27	17	27	30
19[a]	33	27	7	27	8
20[a]	27	29	18	17	20
21[a]	29	35	24		36
22[a]	19	26	3	24	23
23[a]	12	11	10	14	13
Median	24.0	27.0	17.0	20.0	20.0
Mean (SD)	23.9 (6.9)	25.0 (7.6)	14.3 (7.7)	21.0 (5.7)	20.9 (9.8)
Total group (N = 23)					
Median	21.5	19.5	17.0	22.0	18.5
Mean (SD)	20.2 (9.2)	20.8 (9.6)	16.6 (10.9)	18.9 (10.0)	19.1 (10.8)

[a]Morphine responder.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

responders (mean = 23.9, median = 24.0, compared with mean = 19.0, median = 16.5, respectively) and appeared to drop more in the responder group after the morphine dose (Table 4). However, results of the Friedman 2-way analysis of variance by ranks comparing the MADRS score at screening and at the highest dose of each treatment block were not significant.

The most frequent side effects reported in the morphine condition were sedation (N = 10, 44%), dizziness (N = 5, 22%), nausea (N = 6, 26%), and fatigue (N = 3, 13%). The most frequent side effects for the lorazepam condition were sedation (N = 21, 91%), fatigue (N = 5, 22%), dizziness (N = 1, 4%), and nausea (N = 1, 4%). For the placebo condition, the most frequent side effects were sedation (N = 7, 30%), fatigue (N = 2, 9%), and dizziness (N = 1, 4%).

One subject, a 51-year-old woman, was withdrawn from the study after developing substernal and abdominal pain with diaphoresis about 90 minutes after receiving her second week's 30-mg morphine dose. She was transported to the emergency room for evaluation. Results of a physical examination, standard laboratory tests, cardiac enzyme panel, chest x-ray, and electrocardiogram were normal. Sublingual nitroglycerin given twice was ineffective. Her symptoms responded quickly and completely to 2 mg IV of naloxone, an opiate antagonist. She had completed the 2-week placebo block and had only abdominal discomfort after the first week's morphine dose, which she did not bring to the investigators' attention. She had undergone a cholecystectomy several years prior to the study. Angina-like pain associated with narcotic administration in post-cholecystectomy patients has been described[11,12] and is thought to be secondary to narcotic-induced spasms in the sphincter of Oddi. Interestingly, the subject's OCD symptoms responded well to morphine (Table 2, patient 21).

We witnessed no euphoric effects or symptoms of disinhibition in subjects taking morphine or lorazepam. However, several months after completing the study, 1 subject (Table 2, patient 18, a responder) confessed that he had been dependent on and abusing hydrocodone and acetaminophen tablets nearly daily for several years. No other subject exhibited any medication-seeking behavior. The medication-abusing subject claimed that the narcotic reduced his OCD symptoms, which he felt were disabling without it. After confessing, he entered a drug rehabilitation program and was successfully withdrawn. However, within 2 weeks of achieving abstinence he complained of marked worsening of his OCD and returned shortly to illicit hydrocodone use, again reporting reduction in his OCD symptoms.

A second subject (Table 2, subject 2, a nonresponder), unresponsive to fluvoxamine 100 mg/day and risperidone 2 mg/day, experienced a dramatic decrease in horrific images of violence visited upon himself and family members, from many hours per day to less than 20 minutes per day for 3 days after each morphine dose. His other symptoms were not greatly affected. He had no response to lorazepam or placebo. After completing the study, he was treated for 1 year with twice-weekly, oral morphine sulfate 30 mg/day, added to his regular doses of fluvoxamine and risperidone, and exhibited no tolerance, euphoria, or drug-seeking behavior. With this regimen, he maintained the marked reduction in horrific imagery. At the time of writing, he has maintained this improvement for 9 months after discontinuing the morphine augmentation while continuing fluvoxamine and risperidone treatment unchanged.

DISCUSSION

Our data partially support the open-label observations of Warneke[3] and the hypothesis that once- to twice-weekly doses of oral morphine can rapidly, albeit transiently, reduce symptoms in some patients with treatment-refractory OCD. The median decrease in Y-BOCS score after morphine was significantly greater than after placebo, whereas the median decrease after lorazepam was

not. Moreover, the morphine responder who also responded to lorazepam had a much larger Y-BOCS score decrease after morphine (41%) than after lorazepam (27%). Because of the weaknesses of a crossover study design, we examined the results in the first medication condition for all subjects. We observed that subjects who received morphine had a significantly greater reduction in OCD symptom severity (Y-BOCS scores) than those who received either lorazepam or placebo first. This indicates that the greater response to morphine across patients cannot be explained by a carryover effect of lorazepam. This finding also indicates that the greater morphine effect is not due to a natural time-dependent decrease in OCD symptom intensity in those subjects who received morphine later in their sequential trials. Only 7 (30%) of 23 subjects, however, were responders to morphine, and the median decrease in Y-BOCS score after morphine treatment (13%), although greater than that after placebo, was not significantly greater than that after lorazepam (6%). The number of subjects experiencing a > 40% decrease in Y-BOCS score was greater for morphine (5) than for lorazepam (1). In contrast to the results of Warneke,[3] no subject taking morphine in the absence of concomitant psychotropic medication was a responder.

Our study is limited by the small number of subjects, the limited number of exposures to each drug condition, the limited range of drug doses utilized, and the crossover design. Although we did not systematically evaluate the intactness of the blind, only 4 (31%) of the 13 subjects who spontaneously guessed which drug was morphine were correct, an accuracy rate no greater than chance. We cannot be certain that the study methods succeeded in keeping the rating psychiatrists blind to the subjects' study medication status, but we believe they did.

Our study results are also consistent with those of 2 small, double-blind studies of the effects of the mu-receptor (morphine) antagonist naloxone. Insel and Pickar[13] observed exacerbation of OCD symptoms in 2 subjects given intravenous naloxone (0.3 mg/kg). Keuler et al.[14] observed exacerbation in 3 (23%) of 13 OCD subjects administered 0.175 mg/kg in an identical design. The lack of uniformity of response in our study and that of Keuler et al.[14] may reflect a biological heterogeneity in the pathophysiology underlying OCD symptoms. The fact that many OCD patients fail to respond to SSRI treatment certainly suggests such heterogeneity. Pathophysiologic differences (or pharmacodynamic differences) may also explain the transient improvement in OCD symptoms observed in 2 patients with comorbid Tourette's syndrome after a double-blind, intramuscular injection of a much smaller dose of naloxone (0.01 mg/kg).[15] The small number of subjects in all of these studies constrains the interpretation of all of the results.

If there is a true biological mechanism underlying the apparent acute but transient response of OCD symptoms to a single dose of morphine, what might this be? As is well known, medication trials implicate serotonin in the pathophysiology of OCD[1] and imaging studies implicate a brain circuit involving the orbital frontal cortex, anterior cingulate gyrus, striatum (caudate nucleus and putamen), globus pallidus, and thalamus.[3,16] Given this information, one possible biological mechanism is morphine's mu-opioid receptor-mediated disinhibition of midbrain serotonergic neurons in the dorsal raphe nucleus and periaqueductal gray via suppression of inhibitory GABAergic transmission.[17,18] This disinhibition produces an increase in serotonergic tone in the striatum, globus pallidus, and elsewhere that is not unlike that induced by an SSRI. Interestingly, chronic treatment with the SSRI fluoxetine increases the density of cells expressing mu-opioid receptors in areas that are hyperactive in OCD, i.e., the caudate, putamen, and frontal cortex, among other sites.[19]

An alternative explanation would be that mu-receptor agonists like morphine block serotonin-induced release of the excitatory neurotransmitter glutamate in the medial prefrontal cortex (and presumably elsewhere).[20] This is an intriguing finding given the growing speculation that OCD symptoms may reflect, in part, excessive glutamatergic activity.[21–23] The observation that striatal opioid peptides act as negative feedback messengers that decrease output of striatal pathways[24] is consistent with the reported mu-agonist suppression of glutamate release.[20]

A single dose of morphine also affects gene expression. A single dose activates immediate early genes for c-*fos* and jun-B in the dorsal raphe, caudate nucleus, and thalamus.[25–27] A single morphine dose also alters within 30 minutes the expression in the medial striatum of proteins involved in mitochondrial respiration and cytoskeletal functions.[28] To hypothesize the steps in the biochemical cascade that might link activation of c-*fos* and jun-B and changes in striatal neuronal proteins to a decrease of OCD symptoms would involve too many speculations and assumptions to be worthwhile in our present state of knowledge. Still, the acute onset and transience of these genetic effects after a single morphine dose mirror the clinically observed rapid onset and transience of the relief of OCD symptoms that we and others[3] have observed.

CONCLUSION

Our results and those of others[3,4,7,8,13,14] suggest a role for morphine or other mu-receptor agonists in the management of treatment-refractory OCD. The response seen, its rapidity, and the relative tolerability of the treatment are encouraging and warrant larger and longer-term studies. Future trials should also assess the abuse potential of opiates in this patient population. Although we did not witness euphoric effects in any of our subjects, and none reported euphoria, the study's limited duration might

not have been adequate for such complications to become manifest. Drugs with less abuse potential than morphine, such as methadone, a mu-agonist, and buprenorphine, a mixed agonist/antagonist at the mu-receptor, deserve study. The effect of morphine and other mu-receptor agonists on glutamatergic function in brain regions abnormally active in OCD, together with recent evidence suggesting that glutamate may play a role in the pathophysiology of OCD,[21–23] also suggests that the therapeutic potential of glutamate antagonists such as memantine and lamotrigine should be explored.

Drug names: buprenorphine (Buprenex, Subutex, and others), bupropion (Wellbutrin and others), clomipramine (Anafranil and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), hydrocodone and acetaminophen (Vicodin and others), lamotrigine (Lamictal), lorazepam (Ativan and others), memantine (Namenda), methadone (Methadose, Dolophine, and others), morphine (Kadian, Avinza, and others), naloxone (Narcan and others), nitroglycerin (Minitran, Nitro-Dur, and others), risperidone (Risperdal), topiramate (Topamax), tramadol (Ultram and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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