Buprenorphine augmentation in the treatment of refractory obsessive–compulsive disorder

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Abstract:
Background: OCD is often refractory to treatment. There is a need for the development of new, non-invasive treatments for severe OCD.
Rationale: There is evidence that opiates can be a useful adjunctive treatment in OCD. We summarise our experience with sublingual buprenorphine augmentation of standard pharmacological management of severe OCD.
Methods: Patients were recruited from a standard psychiatric outpatient clinic and gave their consent to the treatment trial. The severity of the OCD was rated with the Y-BOCS. The buprenorphine was introduced to their existing medication regime at a low dose and the dose increased according to response. In order to gauge the reproducibility of the response the buprenorphine was withdrawn and then reintroduced once symptoms had returned.
Results: 4 out of 7 patients with treatment resistant OCD showed a 30% reduction in the Y-BOCS score following buprenorphine augmentation. 3 of the responders were co-morbid for other Axis 1 diagnoses. All of the responders had shown some improvement with SSRIs or clomipramine. Non-responders had not shown any improvement with either antidepressant or antipsychotic drugs. Typically improvement appeared within 2 days of initiating buprenorphine and waned within 1 to 2 days of its discontinuation. The dose of buprenorphine required varied between 400 µg and 600 µg a day. One responder managed on alternate day dosing. Reintroduction of buprenorphine resulted in symptom control within 2 to 3 days. The buprenorphine treatment was not associated with significant side-effects and the improvement was maintained without progressive dose escalation.
Conclusions: Buprenorphine augmentation of standard treatment for OCD can result in clinically meaningful improvement in a proportion of refractory OCD cases. Further treatment trials are indicated.

Keywords: obsessive–compulsive disorder, treatment, buprenorphine

Introduction

Obsessive–compulsive disorder (OCD) is a disabling disorder often under recognized and is all too often refractory to treatment. The evidence base supports the use of cognitive behavioural therapy (CBT) with exposure and response prevention as first-line treatment with concomitant treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants for more severe or therapy-unresponsive cases. Treatment with clomipramine and antipsychotic medication is recommended for the most treatment-resistant cases. Despite these manoeuvres, some 40% of cases are treatment resistant, and many become disillusioned with the psychiatric services and are lost to follow up [Heyman *et al.* 2006; Abramowitz *et al.* 2009; Fineberg and Brown, 2011].

The treatment of last resort has been psychosurgery, which can result in substantial improvement in some 50% of cases without significant adverse effects [Jung *et al.* 2006]. More recently, deep brain stimulation has shown promise [de Koning *et al.* 2011], but the procedure is still experimental and is not widely available. Thus there remains a need to further develop minimally invasive

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treatment options for refractory OCD. In this regard there is a small literature supporting the use of opiates in the treatment of refractory OCD [Shapira *et al.* 1997; Warneke, 1997; Goldsmith *et al.* 1999; Koran *et al.* 2005]. In this case series of seven patients with severe, treatment-resistant OCD we present our experience in using buprenorphine to augment antidepressant treatment of their OCD.

Methods

The patients were recruited from a standard psychiatric outpatient clinic. The experimental nature of the proposed treatment was explained to all the participants and all gave their informed consent to participate. Many had been attending psychiatric clinics over several years. The chief criteria for eligibility were severe OCD unresponsive to standard treatment measures which resulted in great personal suffering and extreme limitation in the person's lifestyle. The severity of the OCD was rated using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [Goodman *et al.* 1989]. Three of the patients had other diagnoses in addition to their OCD: one had schizophrenia; one had bipolar 1; and one had attention deficit hyperactivity disorder (ADHD) and dyslexia. Three of the cases will be described in some detail and the remainder in outline.

Sublingual buprenorphine was introduced at 200 μg a day and increased after 1 week to 200 μg twice a day after 1 week. Further 200 μg dose increments were made according to response. The patient's standard medication was not altered. Cyclizine 50 mg three times a day on demand was prescribed in the initial phase of treatment in case the side effect of nausea emerged. To gauge the robustness and reproducibility of the response, buprenorphine was discontinued and then restarted once the symptoms of OCD had returned.

Case reports

Case 1

This patient had had incapacitating OCD and secondary depression for some 60 years. The OCD took the form of her obsessional belief that if she looked at someone, then they would suffer serious harm or even die. This belief rendered her essentially housebound and unable to shop because she would be obliged to constantly retrace her steps to make sure that someone she had passed by in the shop was still alive. At the end of her clinic appointments she would return three or more times to look around the door of the consulting room to reassure herself that the clinician was still unharmed. Over the years she had tried all the available antidepressants and had received electroconvulsive therapy. There was some minimal improvement on high-dose fluvoxamine, which was the antidepressant she was taking when first seen by one of the authors. She was too old to be considered for psychosurgery and did not wish to proceed with this option in any case. A literature search turned up a paper describing the use of morphine in the treatment of refractory OCD [Koran *et al.* 2005] and the patient agreed to give this treatment a trial. Accordingly she was started on oral MST continus 5 mg twice a day. The improvement was remarkable for within a few days she was able to leave her flat, go shopping with a helper, and to start attending a day centre. When the MST was discontinued her symptoms returned and she again became housebound.

She improved again following the reintroduction of MST. At a later date the case was brought to the attention of Professor Nutt [Nutt, 2007], who suggested that the MST be substituted with sublingual buprenorphine. The buprenorphine was substituted for the MST and the dose titrated up to 600 μg a day, which is combined with fluvoxamine 200 mg/day. She is not symptom free, but she is again able to leave her flat, shop and attend a psychiatric day hospital. Her Y-BOCS fell from 40 to 20 following the introduction of buprenorphine.

Case 2

This 45-year-old woman has brittle bipolar 1 and severe OCD. The OCD takes the form of obsessions concerning cleanliness and contamination with corresponding compulsive cleaning rituals. She feels compelled to bleach the toilet seat before and after use, to disinfect the kitchen work tops many times a day, to wash her hands many times a day, she is unable to handle food and prepare a meal for fear of contamination from the food, and is obliged to prepare long 'to do' lists. Her marriage had broken down in part due to the difficulty she experienced in sharing the toilet and bathroom with her husband and son. She was taking lithium carbonate 600 mg, lamotrigine 50

mg twice a day, quetiapine XL 600 mg at night and sertraline 100 mg at night. At times of heightened emotional stress she would experience worsening in her OCD and depressive symptoms, which she would attempt to combat by increasing her sertraline to 150 or 200 mg, a manoeuvre which would improve her OCD but result in her becoming manic. She had participated in a CBT group for people with OCD, which she found supportive without achieving any improvement in her OCD symptoms. She readily agreed to a trial of buprenorphine augmentation. The Y-BOCS score was 33 at the start of the treatment trial. After 2 days of sublingual buprenorphine 200 μg twice a day (also prescribed with on demand cyclizine 50 mg twice a day in case of nausea) she reported substantial improvement in her OCD symptoms. After 1 week the buprenorphine was discontinued and within 2 days her OCD symptoms had returned in full, only to promptly remit again following the reintroduction of buprenorphine. Currently she is being maintained on sublingual buprenorphine 200 μg in the morning and sublingual buprenorphine 400 μg in the evening in addition to her other medications and her Y-BOCS has fallen to 20. Administration of buprenorphine on alternate days was not as effective as daily dosing. She experienced side effects of dry mouth, some difficulty in constructing sentences and spelling, and some episodes of topographical disorientation. These side effects diminished in time and following the withdrawal of the cyclizine. She is a very articulate and literate woman and wrote an account of how the introduction of buprenorphine had affected her: some of her observations are reproduced below.

> This medication is in no way similar to anything else I have been tried on. My personality has been changed and although there have been some side effects, it's the ray of light we've been waiting for.
>
> … whilst in the process of carrying out a ritual, for the first time ever, I began to find it highly amusing. I felt like laughing.
>
> When I'm doing something, my whole attention is taken up with it. There are no lists building up about everything I've got to do next (right down to the last detail).
>
> The psychologist's training has all come back to me now and I think it is impressive. However, at the time I felt it wasn't viable or even relevant and I am now very surprised to find that I've absorbed so much from the course. The problem with the 'Mind Lock' course is that you cannot gain from it when your OCD is extreme; you have to be 'within reach', if you like. This is the hardest part and this new drug could provide the answer.

Case 3

This 44-year-old divorced man had had worsening OCD symptoms from childhood. His childhood had been blighted by emotional neglect and he and his siblings were abandoned by their parents and brought up in care. His life was taken over by obsessional thoughts concerning dirt and contamination with compensatory compulsions of cleaning, checking and mental counting. He also had the compulsion to shave off all his body hair so as to ensure that his person was rendered as germ free as possible. His marriage had broken down as a result of his OCD and he had been unable to work for 12 years on account of his OCD symptoms. He was significantly depressed. Although he was bright, insightful and articulate, his educational attainment was poor and he was unable to read and write, which was probably the result of unrecognized childhood ADHD coupled with emotional abuse and neglect. As an adult he still manifested the ADHD symptoms of fidgeting, poor concentration span and explosive, staccato speech, which rendered him socially awkward and unable to sit still and to watch a TV programme through to the end, although distraction caused by his OCD symptoms also contributed to this difficulty.

At the time of referral he was taking fluoxetine 40 mg daily without any impact on his OCD symptoms (Y-BOCS 36). Increasing the fluoxetine to 60 mg daily did not result in improvement so he was switched to clomipramine and the dose increased in stages to 175 mg at night, but later reduced to 150 mg at night on account of the side effects of postural hypotension. This resulted in significant improvement in his depressive symptoms but made little impact on his OCD symptoms. Quetiapine XL was introduced and the dose increased in stages to 200 mg at night. This resulted in further improvement in his depressive symptoms and some improvement in his OCD symptoms (Y-BOCS 34) in that he was not checking as much and was able to watch TV for longer without being distracted by his OCD. He participated in a CBT 'Brain Lock' group, which he found very supportive, although there were no improvements in his OCD symptoms.

He agreed to a trial of buprenorphine augmentation and was started on sublingual buprenorphine 200 μg twice a day, which after 2 days resulted in substantial improvement in his OCD (Y-BOCS 20). His symptoms returned some 4 days after the buprenorphine was discontinued. Restarting the buprenorphine at a dose of 200 μg once a day resulted in some symptom control after 3 days, but an increase up to 200 μg twice a day resulted in an improvement to the previous best level after another 3 days. Further increases in the buprenorphine dose did not result in further improvement and it was found that alternate day administration of buprenorphine was sufficient to maintain control of his OCD symptoms. He continues to feel compelled to shave off his body hair.

Subsequently his ADHD has been treated with long acting methylphenidate with substantial improvement in his ADHD but without further improvement in his residual OCD symptoms.

Case 4

A 45-year-old divorced man had for many years had the paranoid delusion that people were looking at him and talking about him whenever he was out and about. The belief had not been much improved by the high-dose sulpiride or SSRI that he had been prescribed and, to cope with his symptoms, he had taken to sleeping in the day, only venturing out at night to do his shopping in a 24 h supermarket. Another coping strategy he had devised was to distract himself by mental counting, a strategy which had become so ingrained that it had become a bothersome compulsive ritual, which dominated his waking hours. The substitution of clomipramine for the SSRI resulted in some improvement in his depressive symptoms, and the quality of his sleep, but without improving the compulsive counting. The introduction of buprenorphine at a dose of 200 μg twice a day resulted in an almost complete resolution in his counting ritual, although he still remained as paranoid. Cessation of the buprenorphine resulted in a relapse of his counting compulsion within 4 days. Reintroduction of the buprenorphine resulted in symptom control within 2 days.

Unresponsive cases

Three individuals with severe OCD (Y-BOCS > 35) failed to show any improvement in their OCD symptoms following a trial of buprenorphine. All of these patients were significantly depressed and none had shown significant improvement with multiple treatment trials of different antidepressants or after referral to a CBT group for patients with OCD.

Conclusions

This uncontrolled, naturalistic study suggests that buprenorphine augmentation is a worthwhile manoeuvre in severe, treatment-resistant OCD.

It is worth noting that most of the subjects who responded to buprenorphine augmentation were complex cases and comorbid for other psychiatric diagnoses. They would probably have been excluded from more orthodox treatment trials of OCD, but are likely more representative of the sort of patients seen in an ordinary psychiatric outpatient service. The doses of buprenorphine used are small, typically far less than those used to treat chronic pain, and to date the responders have not required an increase in the buprenorphine dosage to maintain the improvement. One of the responders manages on alternate-day dosing. Withdrawal of the buprenorphine typically results in a relapse occurring within 1–2 days: restarting the buprenorphine achieves symptom control within 2–3 days.

Buprenorphine responders had all shown some improvement in their depressive symptoms with either SSRIs or clomipramine.

The underlying mechanism of opiate-mediated improvement in OCD is probably unknown. A number of earlier studies have suggested the potential importance of the opioid system in OCD and its treatment [Shapira *et al.* 1997; Warneke, 1997; Goldsmith *et al.* 1999] and naloxone has been shown to rapidly worsen OCD symptoms [Insel and Pickar, 1983; Keuler *et al.* 1996].

Studies in mice suggest that agonist-induced head-twitch behaviour mediated through 5-HT2A receptors is antagonized by both SSRIs and atypical opiates and that combination treatment with both classes of agents is more effective than either treatment alone, suggesting a convergence between the serotonergic and opiate systems [Rojas-Corrales *et al.* 2007]. Consistent with this is the finding that the partial agonist effect of

buprenorphine at the μ-opioid receptor releases central nervous system serotonin and dopamine [Urraca *et al.* 2004].

These inferences are supported by the observation that patients who did not respond to buprenorphine had not improved with antidepressants active on the serotonin pathways.

We believe that further treatment trials of buprenorphine augmentation of antidepressant treatment in patients with severe OCD are warranted.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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