

HOW FREQUENTLY ARE ATYPICAL ANTIPSYCHOTICS USED TO TREAT OCD IN A BRITISH COMMUNITY MENTAL HEALTH TEAM?

Mark Agius^{2,3}, Michael Birtwhistle¹, Donald Servant¹ & Rashid Zaman^{2,3}

¹Bedford Hospital, UK

²University of Cambridge Medical School, Cambridge, UK

³Department of Experimental Psychology, University of Cambridge, UK

SUMMARY

Obsessive compulsive disorder (OCD) is a condition with a prevalence of around 1-2% (3-4% in some studies) with a recognised protocol for its treatment produced by the national institute for health and clinical excellence (NICE).

NICE recommends that all patients with OCD are first offered treatment with cognitive behavioural therapy (CBT) concentrating on exposure and response prevention (ERP) before proceeding to selective serotonin re-uptake inhibitors (SSRIs). Treatment may later be augmented with clomipramine and/or an antipsychotic. This study focuses on the biological treatment received after, or in parallel to, the psychological.

We aimed to collate and evaluate the levels of biological treatment currently received by OCD outpatients in the Bedford East catchment area of SEPT. In particular we wished to establish how many of the patients were receiving an atypical antipsychotic as well as maximal SSRIs.

Hence we have attempted to assess the types of treatment received by patients under our care, and the difficulties associated with the treatment of this illness.

Key words: obsessive compulsive disorder – SSRIs - atypical antipsychotics

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INTRODUCTION

Obsessive compulsive disorder (OCD) is a condition with a prevalence of around 1-2% (3-4% in some studies) with a recognised protocol for its treatment produced by the national institute for health and clinical excellence (NICE).

NICE recommend that all patients with OCD are first offered treatment with cognitive behavioural therapy (CBT) concentrating on exposure and response prevention (ERP) before proceeding to selective serotonin re-uptake inhibitors (SSRIs). Treatment may later be augmented with clomipramine and/or an antipsychotic. This study focuses on the biological treatment received after, or in parallel to, the psychological.

AIM

To collate and evaluate the levels of biological treatment currently received by OCD outpatients in the Bedford East catchment area of SEPT.

KEY OBJECTIVE

In particular we wished to establish how many of the patients were receiving an atypical antipsychotic as well as maximal SSRIs.

METHOD

An anonymised database of 45 outpatients with symptoms of OCD was prepared. Treatment groups were identified and the percentage of the cohort occupied by these groups was calculated. The possibilities for increased medication were noted.

The audit was repeated two years later in 2010.

We wished to find out whether prescribing patterns had changed.

The number of patients with a diagnosis of OCD had increased to 53 patients.

RESULTS

In 2007, the treatments recorded were:

- No antidepressants 13%;
- One SSRI, with scope for increase 71%;
- One SSRI, at maximum dose 22%;
- One SSRI, at maximum dose, plus 2nd SSRI 7%;
- Clomipramine, plus antipsychotic 2%;
- One SSRI, at maximum dose, plus Clomipramine 7%;
- One SSRI, with scope for increase, plus antipsychotic 40%;
- One SSRI, at maximum dose, plus an antipsychotic 18%;
- One SSRI, at maximum dose, plus 2nd SSRI, plus antipsychotic 7%;
- One SSRI, at maximum dose, plus Clomipramine, plus antipsychotic 7%.

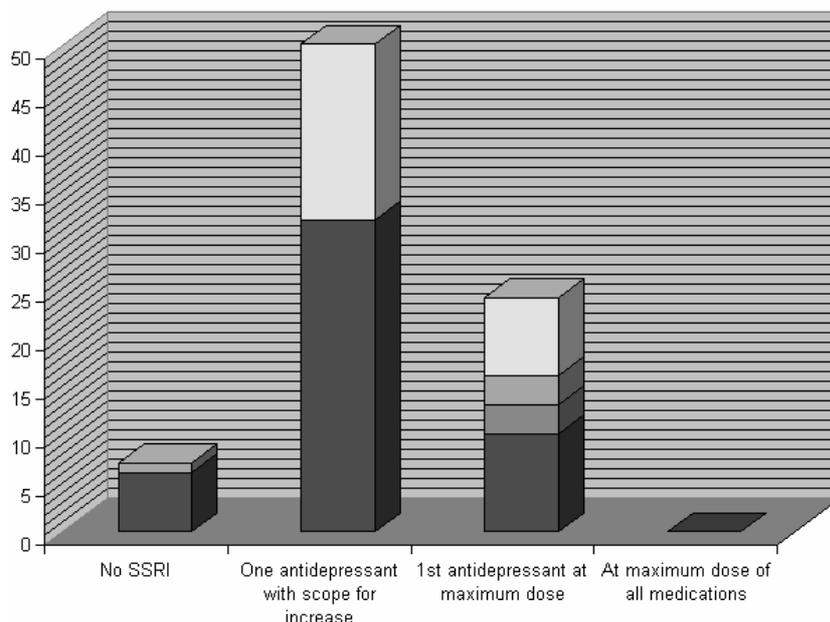


Figure 1. Relationship of prescription of Antipsychotics and antidepressants 2007

By 2010

The audit showed that 23% of the sample had received psychological therapies, 21% had been referred and 55% had neither received nor been referred (Figure 1).

Treatment with antidepressants by 2010 was as follows:

- 34% One SSRI with room to increase dose;
- 26% One SSRI at maximum dose;
- 13% No antidepressant;
- 2% SSRI at maximum plus a second SSRI;
- 4% SSRI plus Clomipramine;
- 9% Clomipramine not maximum dose;
- 9% Venlafaxine alone;
- 2% Amitriptyline alone;
- 2% Two SSRIs;
- 2% Venlafaxine and amitriptyline;
- 2% Clomipramine at maximum dose.

Percentage of patients receiving specific antidepressant

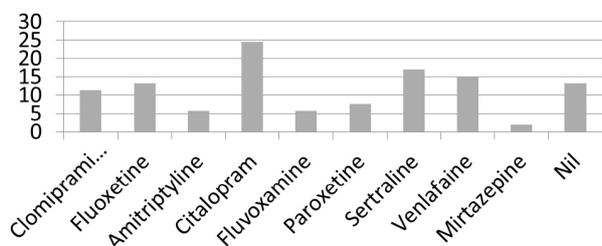


Figure 2. Percentage of Patients prescribed a particular antidepressant in 2010

From the point of view of biological treatment, 23% were receiving neither an SSRI nor Clomipramine. 13% were not on any antidepressant at all. 53% were

prescribed an antipsychotic, while 47% were not prescribed one.

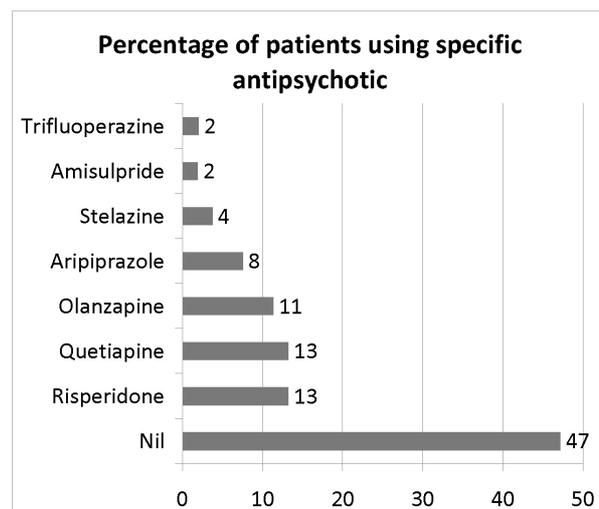


Figure 3. Percentage of patients prescribed a particular antipsychotic in 2010

DISCUSSION

What is the rationale of providing treatment with both SSRIs and Atypical Antipsychotics in OCD?

Obsessive-compulsive disorder (OCD) is a chronic illness associated with substantial morbidity; it often requires long-term medication (Pigott 1999). The first evidence that a serotonergic drug, clomipramine, could be effective in treating symptoms of OCD was published by Fernandez-Cordoba and Lopez-Ibor Alino in 1967 (DeVeugh-Geiss 1994), however controlled trials which demonstrated the efficacy of such pharmacological treatment of OCD only appeared in the 1980s (DeVeugh-Geiss 1994). The observation that

drugs that act by inhibiting serotonin uptake, including clomipramine, fluvoxamine, sertraline and fluoxetine, are effective in treating symptoms of OCD, has led to interest in the role of serotonin in this disorder (DeVeugh-Geiss 1994). Many lines of investigation suggest a serotonergic hypothesis for the pathophysiology and treatment of this disorder (DeVeugh-Geiss 1994). Clomipramine, which is a tricyclic antidepressant which is a potent serotonin uptake inhibitor, was the first pharmacologic treatment for OCD to be studied in large multicentre trials (DeVeugh-Geiss 1994). Subsequently, there have been many trials using selective serotonin uptake inhibitors such as fluvoxamine, sertraline, and fluoxetine (DeVeugh-Geiss 1994). The results from these trials demonstrate that all these drugs are more effective than placebo in treating OCD (DeVeugh-Geiss 1994). However, meta-analysis of the data from controlled trials suggests that the effect size for clomipramine is somewhat larger than that of the selective serotonin uptake inhibitors (DeVeugh-Geiss 1994). Nevertheless, the serotonin uptake inhibitors, while they are effective in a large number of patients, do not appear to provide adequate symptom relief for some patients. Furthermore, even among the patients who do respond to serotonin uptake inhibitors, it is unusual that patients go into complete remission, hence there is the need to further improve the treatment of this disorder (DeVeugh-Geiss 1994).

Several multicentre trials have shown that the selective serotonin reuptake inhibitors fluoxetine, sertraline, fluvoxamine, and paroxetine are both efficacious and have good tolerability in the treatment of OCD (Pigott 1999). However, by contrast, clomipramine, although efficacious, is frequently associated with important side effects, in particular anticholinergic effects (Pigott 1999). Even the supposed superior efficacy of clomipramine can be challenged; thus while 2 recent meta-analyses support the superior efficacy of clomipramine over selective serotonin reuptake inhibitors, 5 of 6 head-to-head comparisons of either fluoxetine or fluvoxamine versus clomipramine have found similar efficacy but a lower incidence of side effects with the selective serotonin reuptake inhibitors in the treatment of OCD (Pigott 1999). It has been reported that a multicentre, 12-week, double-blind trial of paroxetine versus clomipramine versus placebo showed paroxetine to be as effective as clomipramine (Pigott 1999). In this study, paroxetine had significantly fewer dropouts due to side effects than clomipramine, thus demonstrating better tolerability (Pigott 1999). The observation that selective serotonin reuptake inhibitors have similar efficacy to that of clomipramine, and yet have a superior side effect profile, can be expected to importantly modify the treatment of patients with OCD who require long-term treatment (Pigott 1999). Hence, SSRIs are now the first line pharmacological treatment for OCD.

Obsessive-compulsive disorder (OCD) is linked with the serotonin system mainly because of the anti-obsessional efficacy of selective serotonin reuptake

inhibitors (SSRIs) (Denys 2004). However an important limitation of the serotonin hypothesis of OCD is that a substantial number of the patients with OCD do not show significant improvement after an adequate trial with SSRIs (Denys 2004). There is now evidence that these patients may benefit from addition of antipsychotics to their ongoing SSRI treatment, and this therefore suggests that dopamine may also be involved in the pathophysiology of OCD (Denys 2004).

On Neuroimaging, Structural and volumetric abnormalities have been identified in patients with obsessive compulsive disorder (Harsányi 2007). Neuroimaging has also demonstrated dysfunction of these regions in OCD patients. These changes may be summarised as dopaminergic hyperfunction in the prefrontal cortex together with serotonergic hypofunction in the basal ganglia (Harsányi 2007). Thus, dysfunction of the 'cortico-striato-thalamic' loops, in which dopamine is the most dominant neurotransmitter is strongly linked to the symptoms of OCD (Harsányi 2007). These loops are controlled and modulated by ascending serotonergic projections from the raphe nuclei (Harsányi 2007). If serotonergic hypofunction is present, the loops, which are predominantly dopaminergic, became overactive. (Harsányi 2007). It is suggested that this linkage of the two predominant neurotransmitter systems affected in OCD is the reason that SSRIs have limited success alone in the treatment of OCD (Harsányi 2007). Thus it appears that OCD is caused and controlled by the interplay and balance between the dopaminergic and serotonergic systems of neurons in the mentioned areas. As a result, recent international, multicentre studies have addressed the use of antipsychotics in the treatment of the subgroup of SSRI non-responder patients with OCD (Harsányi 2007). Benefit from the use of antidopaminergic substances on the hyperactive cortico-striato-thalamic loops in OCD has been demonstrated by these studies (Harsányi 2007). The investigation of these dysfunctional loops may shed light on the genetic background of OCD, since some of the candidate genes in OCD are coding proteins of the dopamine synthesis (for example: COMT) (Harsányi 2007).

Because of the above, it is now common practice to augment SSRIs and Clomipramine with atypical antipsychotics in the treatment of resistant OCD patients.

Evidence for Augmentation Of SSRIs with Atypical Antipsychotics

An ECNP Consensus statement on Augmentation strategies with antipsychotics (Goodwin 2009) points out that when SSRIs are used as monotherapy it can take as long as 3 months before benefit can be shown (Goodwin 2009). It is advised that antipsychotic addition may be considered in OCD with tic disorder as well as in OCD refractory to SSRIs (Goodwin 2009). In OCD with poor insight, this document advises the treatment of choice to be medium to high dose of SSRI,

while augmentation with anti-psychotics should only be reserved for refractory cases (Goodwin 2009). Augmentation with haloperidol and risperidone is an effective treatment for patients with tics. In refractory OCD, there is data suggesting that there is a specific role for haloperidol and risperidone, while some data suggests that olanzapine and quetiapine can be of benefit (Goodwin 2009).

Sun et al. (2001) reported on two successful treatments of OCD patients not responsive to SSRIs with Risperidone (Sun 2001, Thomsen 2004) reported a series of 17 cases of adolescents treated with Risperidone to augment their SSRI treatment for OCD. Twelve weeks after augmenting treatment, statistically significant improvements were observed in the OCD symptom ratings (Thomsen 2004). In four patients there was moderate improvement, shown by a 25% reduction in Y-BOCS scores in OCD symptoms. Ten patients demonstrated a reduction of 10-25% in the total score, indicating a slight improvement (Thomsen 2004). One patient (6%) had his symptoms reduced from clinical OCD to a subclinical level of OCD symptomatology, and therefore had improved very significantly. No patients had a worsening of OCD symptomatology as a result of augmentation treatment. On the other hand, eight cases suffered weight gain, and four patients reported sedation (Thomsen 2004).

Albert et al. (2002) report that double-blind, placebo-controlled studies have shown the efficacy of adding pindolol (7.5 mg/d), risperidone (2 mg/d) and olanzapine (5-10 mg/d) to SSRIs to augment treatment of OCD (Albert 2002).

Weiss et al. (1999) studied a series of 10 patients with DSM-IV obsessive-compulsive disorder showing significant residual symptoms following an adequate SSRI trial lasting 12 weeks, who were then given olanzapine augmentation for at least 8 additional weeks. The treatment response was measured using the Yale-Brown Obsessive Compulsive Scale as well as the Clinical Global Impressions scale (Weiss 1999). Nine of the 10 patients in this series completed the trial of 8-week augmentation (Weiss 1999). Out of these, 4 demonstrated either complete remission or major improvement in their obsessive-compulsive symptoms, 3 had a partial remission, and 2 experienced no benefit. Only one patient discontinued treatment and sedation was the main side effect reported (Weiss 1999). Based on this data it was concluded that olanzapine can be effective in augmenting ongoing SSRI treatment for a number of patients suffering from obsessive-compulsive disorder who are refractory to SSRI treatment (Weiss 1999).

Matsunaga et al. (2009) compared patients who had responded to SSRIs to patients who had been augmented with three possible atypical antipsychotics. Patients (N = 46) who responded to selective SRIs (SSRIs) over 12 weeks of treatment were continued on SSRI monotherapy as well as receiving cognitive-behavioral therapy (CBT) for 1 year (Matsunaga 2009).

Patients (N=44) who had failed to respond to SSRIs were randomly assigned to 1 of 3 atypical antipsychotics - olanzapine, quetiapine, or risperidone - and were then treated using SSRI + atypical antipsychotics as well as CBT for 1 year (Matsunaga 2009). It was observed that augmentation with atypical antipsychotics reduced Yale-Brown Obsessive Compulsive Scale (YBOCS) total scores in SSRI-refractory OCD patients. However, compared to SSRI responders, total YBOCS scores in those who required augmentation with atypical antipsychotics were higher initially, while they remained at higher levels than those of SRI responders even after 1 year of the treatment (Matsunaga 2009). Thus, patients who required augmentation had been more unwell at the beginning of the study, and, despite improving they remained more unwell than the comparison group at the end of the study (Matsunaga 2009). For this reason, the authors concluded that the study did not sufficiently support the long-term effectiveness of the atypical antipsychotics in the augmentation of SSRIs for treatment-resistant OCD patients. None the less, the authors did find that the approach of augmenting SSRIs with Atypicals appeared useful for some types of OCD patients, particularly those with symmetry/ordering and hoarding symptoms (Matsunaga 2009).

Misri (Misri 2004) studied the use of augmentation of SSRIs or SNRIs with quetiapine in the postpartum period. Twenty-two postpartum women diagnosed with OCD, who had not responded to at least 8 weeks of SSRI or SNRI monotherapy, were offered a trial of quetiapine augmentation for 12 weeks. Response to treatment was assessed using the Yale Brown Obsessive-Compulsive Scale (YBOCS) and Clinical Global Impressions scale (CGI) (Misri 2004). Seventeen patients were included. Three withdrew early due to side effects, and 14 completed the 12-week trial. Out of these, 11 responded to treatment within 12 weeks. There was a mean reduction of YBOCS score of 59.6%. (Misri 2004). This study was not controlled, however it was the first study to demonstrate the effectiveness of quetiapine augmentation of SSRIs in Postpartum patients with OCD (Misri 2004).

Diniz et al. (2010) compared the use of clomipramine to the use of SSRI augmented with Quetiapine, in patients who were resistant to treatment with an SSRI alone. After 12 weeks of treatment with selective serotonin reuptake inhibitor (SSRI) monotherapy with inadequate response, 10 patients were treated with clomipramine and 11 were treated with quetiapine as an augmentation of the SSRI. Outcome was the difference between initial and final scores of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and the score of clinical global improvement (CGI-I) (Diniz 2010). In this study, four out of eleven quetiapine patients and one out of ten clomipramine patients were rated as responders (Diniz 2010). The mean final Y-BOCS score was found to be significantly lower than baseline in the patients augmented with

quetiapine ($P=0.023$), but not in the patients augmented with clomipramine ($P=0.503$) (Diniz 2010). There was a trend towards a significant difference between groups only at week 4 (Diniz 2010). Hence Quetiapine augmentation could be seen to be efficacious in obsessive-compulsive disorder (Diniz 2010). By contrast, Clomipramine augmentation did not produce a significant reduction in Y-BOCS scores (Diniz 2010), however a minority of patients- 4 of 11- did respond to the augmentation. Also the poor response with Clomipramine augmentation does not support the use of Clomipramine as an augmentation of an SSRI, although it continued to be listed in guidelines, including NICE.

Recently, Aripiprazole has begun to be used as an augmenting agent in the treatment of OCD. Delle Chiaie et al. (Delle Chiaie 2011) evaluated the effectiveness and tolerability of Aripiprazole for the augmentation of standard treatments in patients with resistant OCD. Twenty patients with OCD and with a history of resistance to standard pharmacological treatment were included. Aripiprazole was added to ongoing SSRI or clomipramine treatment at a starting dose of 5 mg/day and titrated up to a maximum of 20 mg/day (Delle Chiaie 2011). Efficacy was assessed with the Yale-Brown obsessive compulsive scale (Y-BOCS) and the Clinical Global Improvement-severity scale (CGI-S) at baseline and at week 12 of augmentation with Aripiprazole (Delle Chiaie 2011). All 20 subjects enrolled in this study completed the full 12-week course of treatment. It was observed that there was a significant improvement over the 12-week period. Aripiprazole was generally well tolerated. Thus results suggested that Aripiprazole is effective and well-tolerated as an augmenting agent in patients with treatment resistant OCD (Delle Chiaie 2011).

Selvi et al. (2011) studied the comparative efficacy of aripiprazole and risperidone as augmenting agents in the treatment of obsessive-compulsive disorder patients who did not show a decrease in the Yale-Brown Obsessive-Compulsive Scale after monotherapy for 12 weeks with selective serotonin reuptake inhibitors (SSRIs). Sixty-nine patients were followed up for a 12-week SSRI monotherapy period. Of these, forty-one patients were considered refractory and were randomised to receive either risperidone (20 patients, 3 milligrams daily) or aripiprazole (21 patients, 15 milligrams daily) as augmentation to SSRI treatment. Out of these Sixteen patients (76.2%) in the aripiprazole group and 18 patients (84%) in the risperidone group completed a treatment period of 8-weeks (Selvi 2011). Eight patients (50%) in the aripiprazole and 13 patients (72.2%) in the risperidone group met criteria for response of a Y-BOCS decrease $\geq 35\%$ by the end of the study (Selvi 2011). Therefore it appears that the risperidone group showed a significant improvement in Y-BOCS obsession scores compared with the aripiprazole group. Hence the findings suggest that risperidone may be more effective than aripiprazole in treating refractory OCD (Selvi 2011).

It is important to note that not all patients respond to SSRI augmentation with Atypical Antipsychotics. Sumitani et al. (Sumitani 2006) pointed out that while the addition of a low-dose atypical antipsychotic, such as risperidone, or olanzapine, to ongoing SSRI treatment is often shown to be effective, there are patients who still show no response after trials with this augmentation therapy (Sumitani 2006). Hence they attempted to identify clinical features of OCD patients who showed different responses to pharmacological treatment (Sumitani 2006). They assessed fifty OCD patients, who were divided into three groups according to their pharmacological responses: responders to SSRI (group A: $n=25$), responders to SSRI with an atypical antipsychotic (group B: $n=15$), and non-responders to both SSRI and SSRI with an atypical antipsychotic (group C: $n=10$). The clinical features they examined were age, sex, age of onset, duration of illness, types of obsessive-compulsive symptoms, severity, improvement after treatment, insight into disease, depression, comorbidity, involving family members in compulsive or ritualistic behavior, and the level of social adaptation of each OCD group (Sumitani 2006). They observed significantly lower insight levels in group B and higher depressive levels in group C. OCD patients who were refractory to SSRI mono-therapy were more likely to demonstrate comorbidity. OCD patients in group A, who responded to an SSRI, demonstrated significantly greater improvement, while group B, who responded to SSRI augmented with Atypical antipsychotic, showed inferior social adaptation after treatment (Sumitani 2006). There were no significant differences in age, sex, age of onset, duration of illness, severity, involving family members in compulsive or ritualistic behaviour, and social adaptation before treatment in the three OCD groups (Sumitani 2006). Thus the investigators concluded that there were differences in the clinical features of OCD patients who showed different responses to pharmacological treatment. In other words, it appeared that OCD is clinically and biologically heterogeneous. These results are of clinical importance in explaining why some of our patients seem particularly difficult to treat. Certainly, our own group have found that our patients who have a comorbidity with bipolar disorder and are more difficult to treat (Derby et al. in Press).

In our own Sample,

In 2007, only 7% of patients had one SSRI at maximum dose, plus clomipramine, plus an antipsychotic and even here the dosing of the adjuvants was not maximal. This suggests that in general; biological treatment is not at the optimal for recovery of patients to the point of discharge.

The sample included all patients displaying OCD symptoms, whether or not they also carried one or more axis 1 diagnoses; around half the sample could be said to have “pure” OCD. This produces an apparent

incoherence in treatment strategy and presumably also the lack of clomipramine used as first line adjuvant, despite its place on the NICE guidelines. 7% had a second SSRI instead of the tricyclic and may therefore benefit from a trial, but even among the “pure” patients by no means all had a biological treatment intensity which followed the algorithm. Many patients would benefit from a medication review for treatment optimisation.

In the remainder there was further headroom for increasing biological therapy. 71% were on one antidepressant alone, with scope for an increase in dose. 40% of patients were on one antidepressant, with scope for increase, and had been started on an antipsychotic. 22% had one antidepressant at its maximum, most of these (18% of the total) were augmented by an antipsychotic, 7% with a second SSRI and 7% with clomipramine. No patients had more than one class of medication at maximum.

Psychological therapy should be offered for 10 hours from the start of treatment (NICE) but 13% of patients were still receiving no SSRIs, 2% (one patient) were on clomipramine alone as first line.

In 2010, roughly half the patients in this sample had neither received nor been referred for psychological therapies and that a quarter were on neither an SSRI nor clomipramine. The assumption has been made that these patients are of a severity to warrant both psychological and pharmacological therapy. Judging by the number of patients currently under follow up by the BLPT as outpatients in Bedford East, it appears more should now be receiving higher levels of biological therapy in order for prompt discharge. Confounding factors include the diagnostic mix/uncertainty, the individual tolerance of treatments, tailoring therapies individually for patients (including the level of psychological involvement), the lack of clear NICE guidance for augmentation treatment and the length of time patients have been receiving treatment.

However, it is of interest that the literature suggests that there are certain groups of patients, including those with co-morbidities which are particularly difficult to treat. The group of patients in BECMHT are an extremely heterogeneous group. They include some who have recently come into the service and some who have been in the service for a long time because they are resistant to treatment. Our audit technique is only a sample of how patients were being treated at the time we collected the data. Time in the service was not factored into the assessment.

It may be that some of the results we report reflect the heterogeneity of patients and a concentration effect of refractory patients being concentrated in our team.

CONCLUSION

It would be worth looking into why half have not seemed to enter the system with regards to psychological therapies and whether this is down to a

lack of availability of psychologists, a lack of referring or due to a lack of patients willing to undergo it.

Relatively few of our patients were having maximal SSRI treatment, let alone with an antipsychotic, despite guideline recommendations. There is, therefore, plenty of leeway for the escalation of patients' biological therapy. Given the number of patients currently receiving secondary care, an escalation of their treatment should result in better patient health and a subsequent increase in discharges.

In order to allow a more complete analysis of the situation in a future evaluation, a scale such as Y-BOCS could be used to quantify symptomatology and hence allow comparison of the levels of medication with the illness severity. The data do not account for the individual patient and their preferences, which are negotiated at each consultation in a patient centred manner.

We suggest that a treatment pathway, monitored by serial measurement using Y-BOCS at recurring points along the pathway, should be set up for OCD within SEPT, in order that psychological and biological treatments for OCD should be co-ordinated, and thus treatment be optimised.

REFERENCES

1. Albert U, Bergesio C, Pessina E, Maina G, Bogetto F. Management of treatment resistant obsessive-compulsive disorder. Algorithms for pharmacotherapy. *Panminerva Med.* 2002 Jun;44(2):83-91.
2. Delle Chiaie R, Scarciglia P, Pasquini M, Caredda M, Biondi M. Aripiprazole augmentation in patients with resistant obsessive compulsive disorder: a pilot study. *Clin Pract Epidemiol Ment Health.* 2011;7:107-11.
3. Denys D, Zohar J, Westenberg HG. The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. *J Clin Psychiatry.* 2004;65 Suppl 14:11-7.
4. DeVeugh-Geiss J. Pharmacologic therapy of obsessive compulsive disorder. *Adv Pharmacol.* 1994;30:35-52.
5. Diniz JB, Shavitt RG, Pereira CA, Hounie AG, Pimentel I, Koran LM, Dainesi SM, Miguel EC. Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial. *J Psychopharmacol.* 2010 Mar;24(3):297-307.
6. Goodwin G, Fleischhacker W, Arango C, Baumann P, Davidson M, de Hert M, Falkai P, Kapur S, Leucht S, Licht R, Naber D, O'Keane V, Papakostas G, Vieta E, Zohar J. Advantages and disadvantages of combination treatment with antipsychotics ECNP Consensus Meeting, March 2008, Nice. *Eur Neuropsychopharmacol.* 2009 Jul;19(7):520-32.
7. Harsányi A, Csigó K, Demeter G, Németh A. New approach to obsessive-compulsive disorder: dopaminergic theories. *Psychiatr Hung.* 2007;22(4):248-58.
8. Matsunaga H, Nagata T, Hayashida K, Ohya K, Kiriike N, Stein DJ. A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. *J Clin Psychiatry.* 2009 Jun;70(6):863-8.

9. Misri S, Milis L. Obsessive-compulsive disorder in the postpartum: open-label trial of quetiapine augmentation. *J Clin Psychopharmacol*. 2004 Dec;24(6):624-7.
10. Pigott TA, Seay SM. A review of the efficacy of selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *J Clin Psychiatry*. 1999 Feb;60(2):101-6.
11. Selvi Y, Atli A, Aydin A, Besiroglu L, Ozdemir P, Ozdemir O. The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study. *Hum Psychopharmacol*. 2011 Feb 9. doi: 10.1002/hup.1169. [Epub ahead of print]
12. Sumitani S, Ueno S, Ishimoto Y, Taniguchi T, Tomotake M, Motoki I, Yamauchi K, Ohmori T. Clinical features of patients with obsessive-compulsive disorder showing different pharmacological responses. *Seishin Shinkeigaku Zasshi*. 2006;108(12):1282-92.
13. Sun TF, Lin PY, Wu CK. Risperidone augmentation of specific serotonin reuptake inhibitors in the treatment of refractory obsessive-compulsive disorder: report of two cases. *Chang Gung Med J*. 2001 Sep;24(9):587-92.
14. Thomsen PH. Risperidone augmentation in the treatment of severe adolescent OCD in SSRI-refractory cases: a case-series. *Ann Clin Psychiatry*. 2004 Oct-Dec;16(4):201-7.
15. Weiss EL, Potenza MN, McDougle CJ, Epperson CN. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. *J Clin Psychiatry*. 1999 Aug;60(8):524-7.

Correspondence:

Mark Agius, MD
SEPT at Weller Wing, Bedford Hospital
Bedford, Bedfordshire, MK42 9DJ, UK
E-mail: ma393@cam.ac.uk