TREATMENTS USED FOR OBSESSIVE-COMPULSIVE DISORDER (OCD) – AN INTERNATIONAL PERSPECTIVE

ABSTRACT

Objectives: To assess the different types of psychotropic medication, psychological therapies and novel therapies used in patients with obsessive-compulsive disorder (OCD) in different countries around the world.

Methods: Researchers in the field of OCD were invited to contribute summary statistics on the characteristics of their patients with OCD and the proportion of their samples that had received certain types of treatment. Consistency of summary statistics across countries was evaluated.

Results: The study surveyed 19 expert centres from 15 countries (Argentina, Australia, Brazil, China, Germany, Greece, India, Italy, Japan, Mexico, Portugal, South Africa, Spain, the United Kingdom and the United States of America) with a total sample of 7340 patients with OCD. There was significant variation in the frequency of use and selection of selective serotonin reuptake inhibitors (SSRIs), other antidepressant therapy, antipsychotic medication and mood stabilisers. There was also significant variation in the use and accessibility of exposure and response prevention for OCD. Neurostimulation techniques such as transcranial magnetic stimulation (TMS), deep brain stimulation, gamma knife surgery and psychosurgery were used in less than 1% of the sample.

Conclusions: Consistent with internationally accepted treatment guidelines for OCD, SSRIs were the most frequently used medication. The clear preference for some SSRIs and antipsychotic agents over others may indicate differences in tolerance, efficacy and/or accessibility of certain SSRIs, and this needs further evaluation. Contrary to treatment

guidelines, exposure and response prevention therapy was infrequently used and reported to be difficult to access in most countries.

Keywords: Cross-cultural study, obsessive-compulsive disorder, pharmacotherapy, medication, selective serotonin re-uptake inhibitors, antipsychotics, benzodiazepines.

INTRODUCTION:

Obsessive-compulsive disorder (OCD) is characterised by repetitive and intrusive thoughts, urges, images or fears (obsessions) and repetitive behaviours or mental acts (compulsions). Common symptoms include fears of contamination and excessive hand washing, preoccupation with symmetry and ordering, intrusive and distressing unacceptable or taboo thoughts and repetitive checking. These types of symptoms tend to be similar regardless of cultural background (Matsunaga et al., 2008). Throughout the world, OCD is thought to occur in 0.8 to 2% of the population (Ruscio et al., 2010). It is viewed as a relapsing remitting disorder (Skoog and Skoog, 1999, Eisen et al., 2013) and it has been observed that patients with OCD often do not receive optimal treatment with psychotropic agents (Sorsdahl et al., 2013). Treatment guidelines (NICE, 2005, 2007, Baldwin et al., 2014, Marazziti and Consoli, 2010, Bandelow et al., 2012) recommend selective serotonin reuptake inhibitors (SSRIs) or exposure and response prevention (ERP) as first line treatments. However, response to pharmacological treatment is frequently inadequate (Schruers et al., 2005) and further limited by poor insight, medication non-adherence and/or adverse effects.

Cross-cultural studies of OCD have been encouraged (Stein and Rapoport, 1996) and research assessing international prescribing trends for OCD can inform us whether treatment

preferences vary from one country to another. Building on the findings of a previous international survey (Brakoulias et al., 2016), this study thus aimed to compare the frequencies of psychotropic agent use for OCD across a larger selection of countries with a more specific focus on the different types of SSRI and antipsychotic medication used in each country, the frequency and ease of accessibility of ERP, and the use of novel therapeutic modalities, e.g. transcranial magnetic stimulation (TMS). Based on previous studies, it was hypothesized that a) the use of different types of pharmacological agents for OCD varies significantly between countries (Van Ameringen et al., 2014, Brakoulias et al., 2016), b) those receiving pharmacotherapy would most commonly be receiving selective serotonin reuptake inhibitors (SSRIs) (Brakoulias et al., 2013, Brakoulias et al., 2016), and that there would be low rates of use of ERP in some countries where access to trained therapists is limited and costly.

METHODS:

The author VB wrote to leading international OCD researchers with the aim of having at least one sample from each of the five inhabited continents of the globe represented in a large international survey. The invitation was also circulated to all members of the International College of Obsessive-Compulsive and Related Disorders (ICOCS). Researchers from specialised centres in 15 countries (Argentina, Australia, Brazil, China, Germany, Greece, India, Italy, Japan, Mexico, Portugal, South Africa, Spain, the United Kingdom (UK) and the United States of America (USA)) were asked to complete a standardised data collection sheet using data from their studies. All the studies were approved by their respective Institutional Review Boards. The survey assessed medication use cross-sectionally, upon referral to each research centre. Information was collected regarding the size of the sample, the years in which the sample was assessed, the mean age and gender distribution of the sample, the mean

severity of OCD in the sample, the mode of referral of participants to the study, and the number of patients that were prescribed psychotropic medication. Specific enquiry was made regarding the types of psychotropic agents in the following order: SSRIs, serotonin and noradrenalin reuptake inhibitors (SNRIs), clomipramine, other tricyclic antidepressants, mirtazapine, reboxetine, benzodiazepines, atypical antipsychotic medication, typical antipsychotic medication, sodium valproate, lithium and any other psychotropic medication. There was also specific enquiry in regards to the type of psychological therapy that patients had received and whether patients have received any other biological treatments such as TMS, deep brain stimulation (DBS) or psychosurgery.

The severity of OCD was assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) in all samples and diagnosis of OCD was made with the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID) (First et al., 2007), the Mini International Neuropsychiatric Interview plus version (MINI (Sheehan et al., 1998, Sheehan and Lecrubier, 2010)), or the Anxiety Disorder Interview Schedule for DSM-IV Lifetime version (ADIS) (Brown et al., 1994).

Consistency of summary statistics across countries was assessed using conventional chi-square tests for categorical variables (i.e. gender, referral type, medication usage), and using the Q heterogeneity statistic for continuous variables (i.e. age, YBOCS score). Analyses were performed in SAS version 9.3 (SAS Institute).

RESULTS:

The characteristics of the 19 international centres are shown in Table 1. Samples were collected between 1990 and 2018. They varied significantly on demographic characteristics,

e.g. gender (the sample from Argentina had more men and the sample from Australia had more women) (overall p-value for consistency in gender distribution across counties was <0.001); and age (the sample from the UK was on average 16 years older than the sample from Argentina) (overall p-value for consistency in age distribution across countries was <0.001). OCD severity also differed significantly across sites, with the mean Y-BOCS score of the Argentinian sample (32.0 – extreme range) being 13 points higher than that of the Rio de Janeiro Brazilian sample (19.3 – moderate range) (overall p-value for consistency in Y-BOCS distribution across countries was <0.001). All of the participants in the samples from the UK and the Boston USA centres were referred by a doctor, whereas the majority of the participants from the sample from India (n=547; 68.2%) were self-referred (overall p-value for consistency in referral patterns across countries was <0.001).

Table 2 shows the frequency with which different SSRIs were used in the different countries. Citalopram and fluoxetine were not available in Japan, but all other countries had access to all 6 available SSRI medications. Fluoxetine (n=966, 15.9%) and fluvoxamine (n=886, 14.6%) were the most commonly used SSRI medications and citalopram (n=395, 6.5%) was the least commonly used. There was no obvious pattern in the use of SSRIs among different countries. The Australian sample (n=95; 36.0%) reported a lower rate of SSRI use than the Argentinian sample (n=314; 88.0%). Table 3 shows the frequency of use of other antidepressants and benzodiazepines. Clomipramine use was highest in the Argentinian (n=140; 39.2%) sample and lowest in the German (n=12; 3.1%) sample. In the total sample, benzodiazepines were commonly used (n=962; 16.3%), particularly in the Americas. Table 4 shows that atypical antipsychotics were used in 23.0% (n=1271) of the sample. Use of atypical antipsychotics was highest in Argentina (n=156; 43.7%) and Japan (n=154; 43.3%) and lowest in the Brazilian Consortium (n=72; 7.2%). Less than 5% reported taking typical

antipsychotic agents (n=274), with rates being highest in the Spanish and Mexican samples. Table 5 shows the use of mood stabilisers and novel agents. Lithium was the most frequently used mood stabiliser (n=237, 4.3%). The use of mood stabilisers was highest in Italy. There was some variation in the use of agents such as memantine, inositol, N-acetylcysteine and methylphenidate between countries, but their use was relatively low overall (i.e. 1% or less).

The use of non-pharmacological biological therapies was uncommon. TMS had been reported used in 23 (0.3%) of participants with these coming from Australia, Italy, Japan, Mexico and the USA. Deep brain stimulation (DBS) had been reported in 11 (0.2%) of participants with these coming from Mexico and the USA. Gamma knife surgery was reported in 5 participants (0.1%) with these coming from the Boston, USA site. Psychosurgery was reported in 13 (0.2%) participants from Australia, Mexico and Spain. There were no reports of the use of transcranial direct current stimulation in any of the samples.

Exposure and response prevention therapy (ERP) had been received by 1286 (31.5%) of the 4086 participants for whom this information had been recorded. Most countries described ERP as being available in association with teaching hospitals or specialised clinics, with most acknowledging that access to adequately trained ERP therapists was difficult. Access to ERP trained therapists was only described as “easy” by the Spanish and UK centres. ERP was subsidised in Australia, Germany and the UK. The most commonly used therapy after ERP tended to be cognitive therapy, except for Central and South America where psychodynamic therapy appeared to prevail.

DISCUSSION:

This survey of psychotropic use in almost 7000 participants represents the largest evaluation of prescribing practices for OCD in the literature thus far. In accordance with our first hypothesis, the study shows significant variation in rates of medication use for the treatment of OCD across the eighteen international sites. Consistent with OCD treatment guidelines a large majority of patients reported taking SSRIs, however the proportion of patients who reported having had ERP was relatively low, with comparative proportions reported to having taken antipsychotic medication. Although more specialised OCD treatment centres were sampled with an average Y-BOCS score in the severe range (24.8) and presumed higher levels of treatment resistance, it was surprising to see that reports of the use of ERP and non-pharmacological biological therapies were low.

Although it was reported that the vast majority of participants (n=2445; 77.9%) took psychotropic agents at the time of assessment, rates of medication use were much lower in Brazil and Australia. Possible explanations for this observation include a less severe OCD (and a lower threshold for treatment seeking), less access to a prescriber and/or more access to psychological treatments. In the Italian and Japanese samples where all or almost all patients received medication, the mean Y-BOCS scores were the highest (the mean score was approximately 30), suggesting that patients with more severe OCD may be more likely to be medicated. Also, samples with more contact with a medical practitioner may be more likely to have been prescribed a psychotropic agent than patients not consulted by a doctor. Consulting a doctor for OCD symptoms may be related to socioeconomic or cultural factors, such as whether OCD is viewed as a medical disorder within the individual's society and a reason for consulting a medical practitioner (Mayerovitch et al., 2003). For instance, contamination concerns may be perceived as a cultural or religious manifestation in India,

thus delaying treatment seeking and adequate prescription of drugs (Chakraborty and Banerji, 1975).

As treatment guidelines recommend either ERP or SSRIs as first-line treatments for OCD, treatment with SSRIs might be lower in countries where there is better access to ERP. This may account for the lower rates of pharmacotherapy in Australia, where the costs of consulting a psychologist for ERP are subsidized by the government (Rosenberg and Hickie, 2010, Richards and Suckling, 2009). However, this survey did not specifically assess the number of patients undergoing ERP. In Brazil, the fact that some centres (Porto Alegre and São Paulo) were recruiting OCD patients for CBT trials, coupled with a strong psychoanalytic tradition (Dunker, 2008), may explain a lower rate of the use of pharmacotherapy, although psychoanalytic therapy has not been demonstrated to be effective in OCD.

Although there was a significant variation in the types of medications used for the treatment of OCD across the seven sites, in keeping with current treatment guidelines and in accordance with our second hypothesis, SSRIs were the most frequently used class of pharmacological agents in each site (with the rates ranging from 58.8% in the Australian sample to 95.7% in the Japanese sample). There were significant differences in terms of the second most frequently used class of medication. For instance, in the Japanese, Indian, Australian and South African samples, it was atypical antipsychotics, whereas in the Brazilian sample, it was benzodiazepines. In the Spanish sample, benzodiazepines and clomipramine were the second most frequently used medications and in the Italian sample, it was valproate and atypical antipsychotics.

Clomipramine was the first agent to demonstrate efficacy in the treatment of OCD and its effectiveness has been replicated in numerous trials (Cox et al., 1993). Due to its adverse effect profile, clomipramine is no longer considered first-line pharmacotherapy for OCD (e.g., Bandelow et al., 2008). The frequency with which clomipramine was used varied between the sites in this survey. The infrequent use of clomipramine in South Africa and Japan may be related to pharmacoeconomic and regulatory factors. Clomipramine is more costly in South Africa and it is not licensed as a treatment for OCD by the Japanese authorities. There may also be a higher likelihood of the more prominent adverse effects of clomipramine in Asians. The slow metaboliser phenotype of CYP2C19 is prevalent in the Asian population and associated with a higher rate of adverse effects of clomipramine (Burroughs et al., 2002), adding weight to the argument that pharmacogenomic factors may also play a role in the choice of medication for OCD.

In the Australian and Italian samples, there were higher rates of SNRIs use (see Table 2). As these medications are generally not indicated for OCD, higher rates of comorbid major depression in the Australian and Italian samples may be a possible explanation for this finding, although comorbidity data were not collected. This is supported by the observation that patients in these samples had the oldest mean ages (see Table 1), whereby rates of comorbid mood disorders increase with age (Diniz et al., 2004).

The rates of benzodiazepine use varied from 10.1% in the South African sample to 41.1% in the Brazilian sample. This is more than would be expected, considering that benzodiazepines are not recommended for OCD in treatment guidelines (Baldwin et al., 2014). One possible explanation might be a high rate of comorbidity with anxiety disorders that are generally treated with benzodiazepines. Indeed, over 50% of OCD patients were found in an Australian sample (Brakoulias et al., 2013) to suffer from a co-occurring anxiety disorder. Also, the use

of benzodiazepines among Brazilian OCD patients was predicted by high anxiety levels (Starcevic et al., 2016). Finally, the particularly high rate of benzodiazepine use in the Brazilian sample may be due to their low cost, greater accessibility and high rates of general benzodiazepine use and abuse in Brazil (Kapczinski et al., 2001).

Atypical antipsychotic medication is often used to augment high-dose SSRI therapy of OCD when a partial response has been achieved (Baldwin et al., 2014). In the total sample of this international survey, more than one quarter of patients receiving pharmacotherapy were administered atypical antipsychotics. This finding is similar to that reported by Van Ameringen et al (2014), whereby 30% of participants with OCD received augmentation with atypical antipsychotics. The rate of atypical antipsychotic use was the highest in the Japanese sample (see Table 2). Atypical antipsychotics might have been prescribed more frequently in this sample because OCD was the most severe, with the highest mean Y-BOCS score. It is important to note that the two samples with the highest rates of atypical antipsychotic use (Japanese and Indian) also had the youngest mean ages. Younger samples of people with OCD are likely to consist of more individuals with an earlier age of onset of OCD. Early age of onset of OCD has been associated with comorbid tics, more treatment-resistant illness, poorer insight, more schizotypal traits and higher rates of schizophrenia in first-degree relatives (Catapano et al., 2010, Diniz et al., 2004, do Rosario-Campos et al., 2001). Thus, a greater severity of OCD and its earlier age of onset might have increased prescribers' tendency to administer atypical antipsychotic agents. As atypical antipsychotic medications are expensive and not necessarily subsidized by governments for OCD treatment, economic and regulatory factors may limit their use in different countries.

The rates of mood stabilisers use (sodium valproate and lithium) in the Italian sample were much higher than in all other samples. This is likely to be due to a high rate of comorbid

bipolar disorder in the Italian sample. It has been shown that bipolar disorder and OCD frequently co-occur and that this co-occurrence has negative prognostic and treatment implications (Perugi et al., 2002, Marazziti et al., 2005).

The present study has a number of strengths and limitations. The participation of international centres from the five continents required a simple procedure, which did not allow all the relevant information to be recorded. Therefore, data on the specific medications (e.g., type of SSRIs and atypical antipsychotics) and their doses were not requested. Likewise, data on the use of psychological therapies (e.g., ERP) and conditions co-occurring with OCD were unavailable. Considering that all data were obtained from the specialised centres, the reported use of pharmacotherapy and various classes of medications is not necessarily representative of the prescribing practices by psychiatrists and primary care physicians in each country. As the period of data collection spanned more than two decades, the results may not accurately reflect current prescribing practices. Medications that were developed more recently, e.g. aripiprazole, may be under-represented. Finally, data have been derived from studies with different objectives and different recruitment methods, making the samples from seven countries heterogeneous.

These limitations are largely offset by the fact that this is the first survey of the use of psychotropic agents in a very large number of OCD patients across 15 countries with very different socioeconomic and cultural characteristics. Another strength is that data were collected from the specialised centres in which all patients received a diagnosis of OCD with clinician-administered diagnostic interviews and all were assessed for the severity of OCD by means of the Y-BOCS. As the data arose from the initial assessment on referral to specialised OCD centres, it is likely that participants had already had some treatment trials for their OCD

prior to referral to a specialised centre and that the results reflect treatment for OCD more broadly, rather than reflecting the practices of specialised centres.

CONCLUSION:

In conclusion, the vast majority of patients referred to OCD research centres in seven countries received pharmacotherapy. The most commonly prescribed medications were SSRIs, which is consistent with treatment guidelines for OCD. The significant variation in the rates at which different types of medications were prescribed for OCD may reflect the differences in the severity of OCD, age of onset of OCD, rates of comorbid anxiety and/or mood disorders, pharmacogenomics, cultural expressions and interpretations of distress, local prescribing habits, economic and regulatory factors and access to ERP. The data also suggest that government policy plays an important role in determining the treatment that people with OCD receive. Clinicians and OCD researchers thus have a significant role in advocating for subsidized medication and psychological therapies for OCD. Future cross-cultural studies should collect data on the specific medications, dosages, combinations, rates of remission (and refractoriness), adverse effects, distress levels, costs, specific comorbidity rates and access to effective psychological treatments.

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