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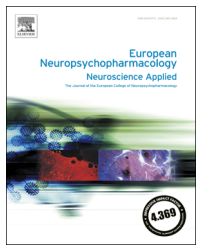

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# Pharmacoepidemiology of obsessive-compulsive disorder: A Swedish nationwide cohort study

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Treatment guideline;
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**Abstract**
The extent to which clinicians adhere to international guidelines for the pharmacological management of obsessive-compulsive disorder (OCD) is unknown. We aimed to comprehensively map the patterns of prescription of psychotropic drugs for OCD patients (adults and children) at the Swedish national level and to compare these prescription patterns to best-practice recommendations in international guidelines. We linked the Swedish National Patient Register and the Swedish Prescribed Drug Register, which includes a record for all medications prescribed and dispensed in Sweden since July 2005. Of all active OCD cases in the Swedish National Patient Register between July 1st, 2005, and December 31st 2008 ($N$=10,523), 85% received at least one psychotropic drug. Most of the medicated adults and children with OCD (88%) received serotonin reuptake inhibitors (SRIs). Of all adults and children prescribed SRIs, 16% received sub-optimal doses. An additional 12% of all medicated patients were prescribed drugs that never included an SRI. Approximately 75% of the patients on SRIs received additional drugs (67% anxiolytics/hypnotics, 27% antipsychotics, 17% serotonin and norepinephrine reuptake inhibitors, 24% other antidepressants). Twelve percent of all medicated patients were at least 'regular' users, and 3% 'heavy' users of benzodiazepines. We also observed important variations in prescription practices according to patient's gender, age, and comorbidity status. We conclude that a substantial number of OCD patients might benefit from changes in their prescriptions. Dissemination of best-practice prescription guidelines for OCD is a major educational goal for the future. Monitoring of these prescription patterns over time is warranted.


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## 1. Introduction

Both international and national guidelines (APA, 2007; Baldwin et al., 2014; Bandelow et al., 2012; NICE, 2005; Statens beredning för medicinsk utvärdering, 2005) recommend cognitive-behavior therapy (CBT) (including exposure and response prevention) and serotonin reuptake inhibitors (SRIs) as first line treatments for adults with obsessive-compulsive disorder (OCD). Children with OCD should be first offered CBT, with SRIs being an endorsed treatment option where CBT fails or in severe cases. However, with only a minority of centers equipped to deliver appropriate CBT, the reality in most parts of the World is that SRIs are often the only realistic treatment option available to clinicians.

Unlike in depression, high doses of SRIs appear more effective than medium or low doses in the first-line treatment of OCD (Bloch et al., 2010). Some guidelines also recommend that patients should remain on pharmacological treatment for at least a year in order to decrease the chances of relapse (APA, 2007; NICE, 2005). Unfortunately, it is estimated that approximately 25–60% of OCD patients do not respond adequately to an initial trial of SRIs (Bandelow et al., 2008; Fineberg et al., 2013; Pallanti et al., 2004). When faced with these circumstances, and in the absence of high-quality CBT, clinicians may adopt various pharmacological augmentation strategies to improve patient outcomes. Augmentation of SRI monotherapy with low doses of antipsychotics has received both the most empirical attention and the clearest endorsement in the available treatment guidelines. Reviews suggest that this approach is superior to the addition of placebo (Bloch et al., 2006; Komossa et al., 2010) and associated with significant response in approximately 30% of SRI-resistant patients (Bloch et al., 2006). Other strategies, such as switching to or adding other SRIs (e.g., clomipramine), or a serotonin and norepinephrine reuptake inhibitor (SNRI) are also often employed, though little evidence (other than anecdotal) supports these strategies (Van Ameringen et al., 2014).

Thus, while there is still some uncertainty regarding the most appropriate augmentation strategies for medication-resistant OCD, broad consensus exists regarding the use of SRIs-preferably at maximum tolerated doses and at least one year's duration-as the first line pharmacological treatment for the disorder. However, the extent to which regular clinicians adhere to treatment guidelines is largely unknown. From a public health perspective, understanding the patterns of drug prescription for OCD at a national level would be invaluable: establishing definitively the extent to which regular clinicians (not necessarily working in specialist clinics) adhere to available guidelines, while also identifying potential areas for improvement (e.g., via targeted training initiatives).

In the current pharmacoepidemiological study we employed the *Swedish Prescribed Drug Register* (SPDR), which includes a record for all medications prescribed and dispensed in Sweden from July 2005, to address two main aims:

1. To comprehensively map the patterns in prescription of psychotropic drugs for OCD patients (adults and children) at the Swedish national level.
2. To compare these prescription patterns to best-practice recommendations in international guidelines.

## 2. Experimental procedures

### 2.1. Swedish registers

Following approval from the Regional Ethics Committee in Stockholm, information was linked at the person level across five Swedish national registers, via the corresponding Swedish personal identity number (Ludvigsson et al., 2009).

The *Total Population Register* contains demographic information on all individuals registered as Swedish inhabitants since 1968. The *Cause of Death Register* includes details on the deaths (e.g., date, primary cause) of all individuals registered in Sweden at the time of death (regardless of whether they were living in the country at this time). In the present study, details from this register were used for two purposes: (1) to identify duplicate personal identity numbers, which may occur when the ID of a deceased individual is recycled, and (2) to ensure individuals were alive during the follow-up period. Where duplicates emerged, the date of death was used to establish the case relevant to the current investigation (e.g., the person living during the period being examined). The *Small Areas for Market Statistics* (SAMS) register includes yearly information of residential location of each Swedish inhabitant. This register allowed us to exclude individuals who had emigrated from Sweden and include individuals who had immigrated to Sweden during the study period. The *National Patient Register* comprises information on all inpatient care and outpatient specialist services in Sweden, with all procedures and primary diagnoses documented per visit for each individual. The register has complete nationwide coverage (since 1987), and of specialist outpatient care since 2001. The *Swedish Prescribed Drug Register* (SPDR) was introduced in July of 2005 and currently includes a record for all medications prescribed and dispensed in Sweden. Information covered in the register includes patient features (e.g., age, sex, region of residence), alongside detailed drug documentation pertaining to the substance administered (registered using Anatomical Therapeutic Chemical [ATC] codes) (WHO Collaborating Centre for Drug Statistics Methodology, 2014), the corresponding dosage and the prescriber's profession and practice.

### 2.2. Diagnostic codes

Patients were defined as all individuals recorded as currently having a diagnosis of OCD (ICD-10 code F42) at least once from the 1st of July 2005 until the 31st of December 2008. While data is available through December 2009, an end date of 2008 was chosen to allow adequate follow-up on the last prescription, in order to determine (1) whether adequate doses had been reached and stabilised and, (2) to further assess whether patients had maintained these doses for the recommended duration of one year.

The ICD codes for OCD in the Swedish National Patient Register have been recently validated (Rück et al., 2015), showing excellent validity, with a positive predictive value (true positives/true positives+false positives) of 91–98% and outstanding inter-rater agreement (Kappa=0.98, $p<0.001$).

We excluded patients who had a lifetime diagnosis of any of the following comorbid conditions that may confound the usual patterns of prescription in OCD: any organic mental disorder (ICD8: 290, 292, 293, 294; ICD9: 290, 293, 294; ICD10: F0), epilepsy (ICD8 and ICD9: 345; ICD10: G40), schizophrenia spectrum disorders (ICD8 and ICD9: 295; ICD10: F20-F29), or bipolar disorder (ICD8: 296.00/.10/.30/.88/.99; ICD9: 296.1/4/5/6/7/8/9; ICD10: F30, F31). Individuals with other mental disorders were not excluded from the analyses. Comorbid depression (ICD8: 296.2; ICD9: 296.2/3; ICD10: F32, F33, F34) and anxiety disorders (ICD8: 300.0/.2; ICD9: 300.0/2; ICD10: F40, F41, F43) were recorded and subject to sub-analyses as their presence may potentially influence the prescription patterns in cases with OCD.