Obsessive-compulsive disorder, serotonin and oxytocin

*To the memory of*
*Börje Wistedt*
*1935 - 2014*
*my mentor in psychiatry*
*always enthusiastic*
*always generous and supportive*

*The truth is rarely pure*
*and never simple.*

*Oscar Wilde*
*1854 - 1900*

*Örebro Studies in Medicine 148*


MATS B. HUMBLE

# Obsessive-compulsive disorder, serotonin and oxytocin
## Treatment response and side effects

*Frontcover photo:* Per Ölund: Tvångsmässiga tennisrörelser [Compulsive tennis movements], gouache (1988)
*Photo:* Edith Humble
*Author portrait photo:* Eva Henriks



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## Abstract

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Obsessive-compulsive disorder (OCD), with a prevalence of 1-2 %, frequently leads a chronic course. Persons with OCD are often reluctant to seek help and, if they do, their OCD is often missed. This is unfortunate, since active treatment may substantially improve social function and quality of life. Serotonin reuptake inhibitors (SRIs) have well-documented efficacy in OCD, but delayed response may be problematic. Methods to predict response have been lacking. Because SRIs are effective, pathophysiological research on OCD has focussed on serotonin. However, no clear aberrations of serotonin have been found, thus other mechanisms ought to be involved.

Our aims were to facilitate clinical detection and assessment of OCD, to search for biochemical correlates of response and side-effects in SRI treatment of OCD and to identify any possible involvement of oxytocin in the pathophysiology of OCD.

In study I, we tested in 402 psychiatric out-patients the psychometric properties of a concise rating scale, "Brief Obsessive Compulsive Scale" (BOCS). BOCS was shown to be easy to use and have excellent discriminant validity in relation to other common psychiatric diagnoses.

Studies II-V were based on 36 OCD patients from a randomised controlled trial of paroxetine, clomipramine or placebo. In study II, contrary to expectation, we found that the change (decrease) of serotonin in whole blood was most pronounced in non-responders to SRI. This is likely to reflect inflammatory influence on platelet turnover rather than serotonergic processes within the central nervous system.

In studies IV-V, we found relations between changes of oxytocin in plasma and the anti-obsessive response, and between oxytocin and the SRI related delay of orgasm, respectively. In both cases, the relation to central oxytocinergic mechanisms is unclear. In males, delayed orgasm predicted anti-obsessive response.

*Keywords*: Adverse effects, Obsessive-compulsive disorder, Orgasm, Oxytocin, Randomised controlled trial, Rating scale, Response prediction, Serotonin, Serotonin uptake inhibitors, Sexual function.

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# List of papers

The following papers form the basis of the thesis:

I. Bejerot, S., Edman, G., Anckarsäter, H., Berglund, G., Gillberg, C., Hofvander, B., Humble, M.B., Mörtberg, E., Råstam, M., Ståhlberg, O. & Frisén, L. (2014). The Brief Obsessive–Compulsive Scale (BOCS): A self-report scale for OCD and obsessive-compulsive related disorders. *Nordic Journal of Psychiatry*, *68*(8), 549-559.
Open access at DOI: 10.3109/08039488.2014.884631

II. Humble, M., Bejerot, S., Bergqvist, P. B. F., & Bengtsson, F. (2001). Reactivity of serotonin in whole blood: relationship with drug response in obsessive-compulsive disorder. *Biological Psychiatry*, *49*(4), 360-368.

III. Humble, M., Bejerot, S., & Bergqvist, P. B. F. (2002). Reactivity of serotonin in whole blood: response to Mulder et al. *Biological Psychiatry*, *51*(3), 267-268.

IV. Humble, M. B., Uvnäs-Moberg, K., Engström, I., & Bejerot, S. (2013). Plasma oxytocin changes and anti-obsessive response during serotonin reuptake inhibitor treatment: a placebo controlled study. *BMC Psychiatry*, *13*(1), 344.
Open access at DOI: 10.1186/1471-244X-13-344

V. Humble, M. B., & Bejerot, S. (2016). Orgasm, serotonin reuptake inhibition and plasma oxytocin in obsessive-compulsive disorder. Gleaning from an early, randomized clinical trial. *Sexual Medicine*, pii: S2050-1161(16)30023-X.
Open access at DOI: 10.1016/j.esxm.2016.04.002

# List of abbreviations

The following abbreviations appear throughout the thesis.

| | |
|---|---|
| 5-HIAA | 5-hydroxy-indole acetic acid |
| 5-HT | 5-hydroxy-tryptamine (= serotonin) |
| ADHD | Attention deficit hyperactivity disorder |
| ANOVA | Analysis of variance |
| APA | American Psychiatric Association |
| ASD | Autism spectrum disorders |
| ASEX | Arizona Sexual Experience Scale |
| ATD | Acute tryptophan depletion |
| BOCS | Brief Obsessive Compulsive Scale |
| CANS | Childhood acute neuropsychiatric symptoms |
| CBT | Cognitive behavioural therapy |
| CGI | Clinical Global Impression |
| CGI-I | Clinical Global Impression – Improvement |
| CGI-S | Clinical Global Impression – Severity of Illness |
| CMI | Clomipramine (= Chlorimipramine) |
| CNS | Central nervous system |
| CPRS | Comprehensive Psychopathological Rating Scale |
| CSF | Cerebrospinal fluid |
| CY-BOCS | Children's version of Y-BOCS |
| DBS | Deep brain stimulation |
| *df* | Degree of freedom |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DY-BOCS | Dimensional Yale-Brown Obsessive Compulsive Scale |
| ECT | Electroconvulsive therapy |
| FDA | Food and Drug Administration |
| fMRI | Functional magnetic resonance imaging |
| GAF | Global Assessment of Functioning |
| GWAS | Genome wide association study |
| HAGS | High-functioning Autism/Asperger syndrome Global Scale |
| HPLC | High-performance liquid chromatography |
| HSD | Honestly significant difference |
| ICD | International Classification of Diseases |
| IQR | Interquartile range (1$^{st}$ and 3$^{rd}$ quartiles) |
| MADRS | Montgomery Åsberg Depression Rating Scale |
| MAO | Monoamine oxidase |

| | |
|---|---|
| MAOI | Monoamine oxidase inhibitor |
| MeSH | Medical subject headings |
| MINI | MINI-International Neuropsychiatric Interview |
| MOCI | Maudsley Obsessive Compulsive Inventory |
| MW | Mann-Whitney U-test |
| NIMH-GOCS | National Institute of Mental Health Global Obsessive-Compulsive Scale |
| OCD | Obsessive-compulsive disorder |
| PANDAS | Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection |
| PANS | Paediatric acute-onset neuropsychiatric syndrome |
| PET | Positron emission tomography |
| PGE | Patient's Global Evaluation |
| PLC | Placebo |
| PMDD | Premenstrual dysphoric disorder |
| PVN | Paraventricular nucleus |
| PXT | Paroxetine |
| PXOS | The Paroxetine OCD study (Zohar & Judge 1996) |
| RCT | Randomised controlled trial |
| ROC | Receiver operating characteristics |
| SCAN | Schedules for Clinical Assessment in Neuropsychiatry |
| SCID | Structured Clinical Interview for DSM |
| SERT | Serotonin transport protein |
| SNP | Single nucleotide polymorphism |
| SON | Supraoptic nucleus |
| SPECT | Single-photon emission computed tomography |
| SRI(s) | Serotonin reuptake inhibitor(s) |
| SSCL | Sexual symptom checklist |
| SSRI(s) | Selective serotonin reuptake inhibitor(s) |
| STI | Serotonin transporter inhibitor (=SRI) |
| SUI | Serotonin uptake inhibitor (=SRI) |
| TCA | Tricyclic antidepressant |
| TPH1 | Tryptophan hydroxylase 1 |
| TPH2 | Tryptophan hydroxylase 2 |
| WB-5HT | Serotonin in whole blood |
| WFSBP | World Federation of Societies of Biological Psychiatry |
| WHO | World Health Organization |
| Y-BOCS | Yale-Brown Obsessive Compulsive Scale |
| Y-BOCS-II | Yale-Brown Obsessive Compulsive Scale, 2nd Edition |

# Preface

The planning of the research projects that form the basis of the present thesis was initiated around 1990. At that time, researchers at the Department of Psychiatry at Danderyd Hospital, Karolinska Institutet, had been conducting research in the field of serotonin-related psychopharmacology for more than a decade. This included investigations of the clinical and biochemical effects of zimelidine, the first selective serotonin reuptake inhibitor (SSRI), and clomipramine, the first potent serotonin reuptake inhibitor (SRI). The focus of these studies was not only depression but also anxiety disorders (Åberg & Holmberg 1979, Koczkas et al. 1981, Åberg-Wistedt et al. 1982, Ross & Åberg-Wistedt 1983, Humble et al. 1986, Humble et al. 1988).

Clomipramine was a European drug, launched by the Swiss company Geigy in 1966, and zimelidine was a Swedish drug, mainly developed at Astra in Södertälje, based on a hypothesis of Arvid Carlsson (Berntsson, Carlsson & Corrodi 1972, Carlsson & Wong 1997). The Food and Drug Administration (FDA) of the USA did not approve clomipramine until 1990, and before this, it was not marketed there (however, for some patients it was clandestinely brought in from Canada).[1] Zimelidine, unfortunately, was withdrawn from the market after less than two years in 1982, due to rare cases of Guillain-Barré syndrome (Fagius et al. 1985), and never reached the American market. Accordingly, the proponents of the serotonin hypothesis of depression were mainly Europeans (e.g. van Praag et al. 1970, Åsberg et al. 1976), while US researchers focussed more on norepinephrine (e.g. Schildkraut et al. 1978). The beginning of the mental shift regarding serotonin and depression in the USA actually seems to have coincided with the years when the American company Eli Lilly were developing fluoxetine. This became the first SSRI marketed in the USA, and at the same time, since clomipramine was still unavailable, fluoxetine became the first SRI available to clinicians in the USA. Fluoxetine was launched in 1988 as Prozac.

The concept of SSRIs being effective also in anxiety disorders, however, was still highly controversial. For this concept to be accepted in the USA, the close analytical observations of his own patients that Peter Kramer communicates in his book "Listening to Prozac" (Kramer 1993), seemingly, were more effectively convincing than much of the research that had

[1] Donald F. Klein, oral communication 1987.

been produced. Nevertheless, several European psychiatrists (Hoes et al. 1980, Koczkas et al. 1981, Modigh 1987, den Boer & Westenberg 1988, Humble et al. 1989, Humble & Wistedt 1992) had already identified the important role of serotonin in anxiety disorders, thereby enabling alternatives to the benzodiazepines, which at that time were unchallenged as pharmacotherapy for anxiety disorders.

In this scenario of the late 1980s, Smith-Kline-Beecham Ltd prepared themselves for an international, multi-centre, clinical trial of pharmacotherapy for obsessive-compulsive disorder (OCD) in collaboration with Novo Nordisk Pharma, manufacturers and marketers of paroxetine, one of the next marketed compounds from the SSRI group.[2] The company had realised that the market for SSRIs was wider than only depressive disorders, and obviously, their strategy was to encompass as many indications as possible. In view of the accumulating data on a link between anti-obsessive effects and serotonin (see 1.5.3.1), OCD was an obvious target. In addition, since researchers at our unit had specific interest, knowledge and experience in the field of serotonergic psychopharmacology, the companies probably saw us as suitable collaborators.

At that time, the access to scientific methods for investigating psychiatric disorders was much more limited than presently, e.g. no access to functional magnetic resonance imaging (fMRI) or positron emission tomography (PET), and genetic analyses were uninformative, time consuming and costly. The incentives of the pharmaceutical companies were merely to provide the evidence of efficacy, necessary for authority approval of OCD as a new indication for paroxetine. At our research facility at the Department of Psychiatry at Danderyd Hospital, however, we negotiated with the companies, who finally allowed us to include some investigations of our own choice, in addition to the assessments and safety checks that were mandatory in the multicentre trial. Significantly contributing to the success of these negotiations were the late Associate Professor Börje Wistedt (1935 – 2014, then head of the Department of Psychiatry at Danderyd Hospital), my co-author Susanne Bejerot and Dr Jan K. Öhrström, then at Novo Nordisk A/S.

[2] Paroxetine was originally synthesised 1975 by Jørgen Buus-Lassen at the Danish pharmaceutical company Ferrosan, but the drug was then transferred to Novo Nordisk A/S, Smith-Kline & Beecham and finally Glaxo-Smith-Kline. Our first contacts for planning our participation in the OCD study were with Novo Nordisk, but Smith-Kline & Beecham later replaced them.

Based on this, and in collaboration with laboratory researchers, we endeavoured to participate in this multi-centre trial and, at the same time, test some biochemical hypotheses regarding response mechanisms in the pharmacological treatment of OCD. Susanne Bejerot was the primary investigator at our centre. She was responsible for inclusion of cases and she personally assessed the majority of the patients. Most of the patients were recruited through advertisements in local newspapers. Data from this trial form the basis for papers II – V in this thesis.

A peculiar feature of this OCD trial was the recording of side effects. The common practice in trials of this type was to let the clinician ask an open question at each visit: "Did you experience any adverse experiences, new symptoms or change of bodily functions since last visit?" Any endorsed symptoms were then categorised concerning the type of adverse experience, their timing, their severity and the estimated likelihood that they were related to the drug treatment. This practice was followed in the trial, but in addition, a new, specific scale "The limited symptom checklist" was introduced. This 14 item rating scale should quantify in a more methodical way some anticipated, specific side effects that were believed to be related to the serotonergic activity of the drugs (in addition to paroxetine and placebo, clomipramine was used as reference active control treatment), and 8 of the items concerned sexual function (for details, see 3.2.5.1). In 1989, the first cases of anorgasmia in fluoxetine-treated patients had been reported. Previously, however, the group of Isaac Marks had described in detail the sexual side effects of clomipramine (Monteiro et al. 1987), and many clinical psychiatrists (including us) were well acquainted with these. Assumedly, the company was expecting that the results of this scale would provide clear evidence that paroxetine had less sexual side effects than clomipramine. Probably, this was not the case, but we do not know, since, to our knowledge, the multi-centre results of this scale were never published. In fact, a paradoxical result of using this extra scale seems to have been a decrease of reported sexual side effects within the conventional adverse effects recording. Few patients endorsed sexual side effects on the open questioning, when they had already been carefully questioned on these functions. In the published report (Zohar & Judge 1996), nothing is mentioned concerning sexual side effects, and, during an international symposium in 1995, one lecturer was intrigued to find that OCD patients seemed to have significantly less sexual side effects from paroxetine than other groups of patients. This was obviously not the case, which we have shown in paper V. In this article, we have made use of the

detailed information on sexual function that we collected by means of the "Limited symptom checklist".

In collaborative trials with academic researchers and pharmaceutical industry, there is always an agreement on how to handle the data. Our agreement included the condition that the company had to approve any publications based on the data. Considering the time that has elapsed since the trial took place, we felt free to forego this.

At the time of this trial, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a rating scale for OCD, was brand new, and due to its apparent advantages compared to previous scales, it was included as the primary efficacy variable. The Y-BOCS has become the gold standard of OCD assessment, but some of its shortcomings became evident during the course of our initial study and thereafter, when assessing OCD patients in clinical practice. This gave rise to the idea of developing an alternative scale for OCD assessment, better suited for routine, psychiatric, clinical practice. Susanne Bejerot's work with this resulted in the Brief Obsessive Compulsive Scale (BOCS), which was first presented in 2002 (Bejerot 2002). It has since been disseminated for free in a Swedish and an English version. In Sweden, it has now been used in adult psychiatry as well as in child and adolescent psychiatry for more than a decade. However, psychometric data testifying on reliability and validity of this scale has been wanting. Through the kind cooperation of researching clinicians using the scale, we are now able to present such data on the BOCS scale as paper I.

Thereby, I have done my utmost to utilise, analyse and publicise the information and the data that we gathered from all the patients that patiently participated in all kinds of interviewing, assessments, questionnaires, blood sampling, etcetera, to which we exposed them. My hope is that this work will somehow contribute to a better situation for those afflicted with OCD.

# 1 Introduction

## 1.1 Obsessive-compulsive disorder – a brief presentation

Obsessive-**compulsive** disorder (OCD) is a psychiatric disorder with variable course and severity and a worldwide prevalence of at least 1-2 % (Ruscio et al. 2010). The pathognomonic symptoms of this disorder are obsessions and compulsions. Obsessions are usually defined as unwanted, upsetting, disturbing or time-consuming thoughts, ruminations or imagery that appear repeatedly and interfere with other activities. Compulsions are repetitive, more or less complex actions or rituals (behavioural or mental) that often may seem as a response to a corresponding obsession, but is in fact exaggerated or pointless and meets no rational purpose. The most common themes of obsessions and compulsions are contamination/cleaning, symmetry/ordering, causing harm/checking and taboo thoughts. Most patients are aware of the irrational nature of these thoughts and actions, which often imposes additional distress.

A considerable proportion of OCD patients have an early onset, i.e. before puberty, and the disorder may lead a chronic, unremitting course; however, waxing and waning courses are common and spontaneous remissions do occur; in a 40-year follow-up of OCD, 20 % had remitted (Skoog & Skoog 1999).

OCD was previously thought to be a rare disorder, for which unfortunately no specific treatments were available. Between 1970 and 1980, however, the advent of two specific treatments, behavioural therapy with exposure and response prevention and pharmacotherapy with clomipramine (a potent serotonin reuptake inhibitor (SRI)), improved the prospects of a positive outcome dramatically. Due to the, at that time, uniquely serotonergic biochemical profile of clomipramine, subsequent research on the psychopharmacology and neurochemistry of OCD has mainly focussed on the monoamine serotonin. Later the selective serotonin reuptake inhibitors (SSRIs) were introduced and likewise found to be effective in OCD, increasing the applicability of pharmacotherapy, due to their more favourable side effect profile. However, a considerable proportion of OCD patients does not respond to the SSRIs or to clomipramine and patients commonly refuse to participate in behavioural therapy. Accordingly, severe OCD cases may still constitute exceptionally demanding therapeutic challenges.

Concerning the biochemistry of OCD, decades of dedicated attempts to find evidence of a purported primary disturbance of the serotonergic system have left disappointingly few unambiguous results. Furthermore, no consensus exists concerning which effects, downstream of the SRI-induced changes of serotonin availability that are involved in the clinical benefit. Hence, our knowledge is clearly insufficient concerning the biological/neurochemical basis of individual response *versus* non-response to anti-obsessive pharmacotherapy with SRIs.

## 1.2 History of OCD concept

Nobody knows whether prehistoric humans may have suffered from OCD or not. However, at present time, this disorder seems rather evenly distributed among various ethnic groups, supporting the notion that OCD probably did exist among our early ancestors.

In ancient religious traditions, typical obsessions have been repeatedly identified and documented (Hermesh et al. 2003, de Silva 2006). Interestingly, this is the case in Christian and Judaic, as well as in Moslem traditions. Religious counsellors have realised that compulsive religious practice often becomes counterproductive, why some of them saw the need to identify this among their followers (Greenberg & Shefler 2008, Avgoustidis 2013).

From the 19th century, OCD is repeatedly described in the psychiatric literature. The French psychiatrist Pierre Janet described 236 cases of OCD or *folie de doute* in connection with psychasthenia (Janet & Raymond 1903), and many regard this as the most perceptive early description of OCD. However, among these cases Janet included not only OCD but also panic, phobic and tic disorders, hypochondriasis and even epilepsy. The hypotheses on OCD aetiology that Sigmund Freud first put forward in his outstandingly detailed single case study, "The Rat Man" (Freud 1909), have not won general acclaim, in spite of the author's highly perceptive clinical observations. However, from this time and onwards, the most common designation of OCD was "obsessive-compulsive neurosis" or "anancastic neurosis". This concept was included among "neurotic disorders" in previous editions of the International Classification of Disease (ICD) of the World Health Organization (WHO), as well as the first two editions of Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association (APA) and the "Diagnostic criteria for research" (Feighner et al. 1972). In DSM-III (APA 1980) and

in ICD-10 (WHO 1992), however, the word "neurosis" was replaced by "disorder", in order to avoid unsubstantiated inferences on aetiology.

## 1.3 Diagnostic definition of OCD

### 1.3.1 Delineations of OCD versus other disorders

OCD in its typical form is easy to identify and distinguish from most other mental disorders. For instance, extensive handwashing will always be a symptom of OCD, whereas social withdrawal could be a symptom of social anxiety disorder, autism spectrum disorder, major depression or schizophrenia. In a number of circumstances, however, the delineation of OCD from other psychiatric disorders may be less clear-cut.

For instance, when the first studies of clomipramine in OCD treatment had appeared, a common opinion was that the individual cases that responded actually suffered from a depressive disorder. At that time, the concept of "masked depression" was broadly recognised, indicating that in some cases of depression, other coexisting symptoms (mental or somatic) were prominent to the extent that the depressive symptoms were overshadowed, and the patients became misdiagnosed (Vanggaard 1976, Kielholz 1979). If such cases had an OCD-like symptomatology, clinical response to a drug, classified as an antidepressant, was not surprising, rather supporting this concept (Marks 1983). The circular nature of this reasoning gave rise to a number of studies to test the concept (e.g. Montgomery 1980, Stern et al. 1980, Mavissakalian et al. 1985, Katz & DeVeaugh-Geiss 1990). Taken together, they strongly support that initial low mood is not a prerequisite for anti-obsessive response, that anti-obsessive response is unrelated to the degree of depression and that separate mechanisms are involved in these effects; findings that challenge the masked depression hypothesis. On the other hand, patients with OCD often report depressive symptoms, and both dysthymia and major depressive episodes are relatively common as co-morbid disorders (Besiroglu et al. 2007).

Another diagnostic uncertainty concerns patients lacking insight that their obsessions and compulsions are irrational. Some patients with poor insight have obsessions that, when disclosed, may appear as bizarre delusions. Previously, such patients might have received diagnoses such as paranoid psychosis or delusional disorder. Several clinical properties of these patients, however, support that they belong to the OCD spectrum; it is, however, likely that they represent a link to schizophrenia spectrum

concerning both aetiology and impairment (Gross-Isseroff et al. 2003, Poyurovsky & Koran 2005). A diagnostic specifier concerning degree of insight is now generally acknowledged by OCD researchers and clinicians (see further 1.4.3).

The compulsions of OCD patients can sometimes be difficult to differentiate from tics. The tics in Tourette syndrome sometimes become elaborated and complex; conversely, some compulsions are quickly performed, in a tic-like fashion.

All the above issues have been more or less resolved by prudently implementing the concept of co-morbidity. The seemingly heterogeneous nature of OCD also suggests the need for subtyping; see 1.4.

### 1.3.2 Diagnostic criteria and classification of OCD

The diagnostic criteria that first came to widespread use were those adopted in the DSM-III (APA 1980). Some important changes appeared in the DSM-III-R (APA 1987), but throughout the evolvement since DSM-III-R, the criteria for OCD in DSM-IV (APA 1994) and DSM-5 (APA 2015) have remained essentially unchanged. One change in DSM-5, however, is that hoarding as the main symptom (previously accepted as a symptom of OCD) now is separated as "Hoarding disorder". Another change in the nosological hierarchy of DSM-5 is that OCD has been separated from the anxiety disorders (where it belonged in DSM-IV). Even if anxiety often is a prominent symptom of OCD, various arguments led the DSM-5 committee to introduce a new category, "Obsessive compulsive related disorders", separate from anxiety disorders. Accordingly, DSM-5 classifies OCD together with "Body dysmorphic disorder", "Hoarding disorder", "Trichotillomania (hair pulling disorder)", "Excoriation (skin picking) disorder", "Substance/medication-induced obsessive-compulsive and related disorder", "Obsessive-compulsive and related disorder due to another medical condition", "Other specified obsessive-compulsive and related disorder" and "Unspecified obsessive-compulsive and related disorder" as a group by its own, neither neurotic nor anxious.

Within the ICD system, criteria for diagnosis of OCD first appeared in ICD-10 (WHO 1992). Here, OCD is classified under the category of "Neurotic, stress-related and somatoform disorders" together with phobias and other anxiety disorders. However, major changes of this nosological classification are proposed for the forthcoming ICD-11 (Stein et al. 2016).

## 1.4 Many approaches to subtyping OCD

Over the years, many researchers (for reviews, see Lochner & Stein 2003, Leckman et al. 2010 and Murphy et al. 2010) have attempted to identify and delineate subtypes of OCD. Some have gained entrance into official classifications; others have not. Generally, the purposes may have been to assist in the choice of treatment or to approach a classification that considers differential aetiology.

### 1.4.1 Obsessions versus compulsions

In the ICD-10 classification (WHO 1992), the following subtypes are included: "Predominantly obsessional thoughts or ruminations", "Predominantly compulsive acts (obsessional rituals)" and "Mixed obsessional thoughts and acts". The balance of the symptom burden between obsessions and compulsions has been thought to be important, e.g. since differential response to treatment modalities was sometimes documented. However, the differential response has been refuted by later research (Foa et al. 1995), the very existence of "pure" obsessional OCD has been questioned (Williams et al. 2011), and in clinical practice, it is often difficult to disentangle obsessions from compulsions. This is e.g. often the case with mental rituals and reassurance seeking. Robbins et al. (2012) even claim that obsessions may constitute *post hoc* rationalisations of primary compulsive urges. Consequently, these authors suggest that OCD is a misnomer and that the name should be changed to compulsive-obsessive disorder (COD). In any case, patients with only obsessions or only compulsions are rare, to the extent that reconsidering the OCD diagnosis in these cases has been suggested (Shavitt et al. 2014). Accordingly, this subtyping of OCD in the ICD-10 is proposed to disappear in the upcoming ICD-11 classification (Stein et al. 2016).

### 1.4.2 With versus without tics

Tic-related OCD has become a widely accepted sub-type, e.g. it is a "specifier" in DSM-5 (APA 2015). It has been reported to constitute 10 - 40 % of the childhood-onset OCD population (Hemmings et al. 2004, Leckman et al. 2010). Tic related patients are more often males and have more symmetry and counting compulsions compared to other OCD patients. In a biochemical study (Leckman et al. 1994 a), the relation between oxytocin and OCD severity differed between patients with and without tics.

### 1.4.3 Poor insight, schizotypal, autistic dimension

OCD with schizotypal traits has been viewed as rather treatment resistant and has regularly been excluded from treatment trials. However, according to Bejerot (Bejerot et al. 2001, Bejerot 2007), this subtype is identical to an autistic traits subtype, which may constitute approximately 15% of the clinical OCD population. Notably, 25% of the autism group has a comorbid OCD. Typical features of the autistic subtype are the need of "just right feeling" and symmetry, similarly to the tic subtype. A subtype with poor insight has also been included as a specifier in DSM-IV (APA 1994) and DSM-5 (APA 2015). However, the degree of insight seems to be linked to the overall OCD severity (Jacob et al. 2014, Shavitt et al. 2014). In addition, many patients with OCD probably have some degree of impaired insight at the very moment when they experience their obsessions (Shimshoni et al. 2011).

### 1.4.4 Early versus late onset

It has been noted for a long time that childhood onset OCD differs in several ways from adult onset OCD. There have been different opinions on where to draw the limit between these two, however, but the most reasonable seems to be to use puberty (Leckman et al. 2010). Among those with early onset, boys are in a clear majority; after puberty, however, females are somewhat more common than males. Presumably, this and other differences between the two groups support differential contributions of various aetiological factors in relation to age at onset. Why, then, would the influence of such aetiological factors change dichotomously at a certain age, and which factors would be liable to such change? The question is still open, but endocrine changes related to puberty are likely candidates to explain this. To the extent that immunological factors are involved in OCD, an alternative explanation might be that the decrease over the life span of thymus capacity for schooling T-lymphocytes (Steinmann et al. 1985) is reinforced during the years around puberty, due to the influence of gonadal steroids (Hince at al. 2008).

### 1.4.5 OCD "Dimensions"

The various targets of obsessions and compulsions have been used to form a categorisation of OCD patients. Based on the symptom check list of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), exploratory multivariate statistics (mainly rotational factor analysis) have been used to identify themes of obsessions and compulsions that commonly appear together (for

a meta-analysis, see Bloch et al. 2008). The factors that usually have emerged (labelled "dimensions") are: (1) aggression, (2) sexual/religious, (3) symmetry/ordering/arranging, (4) contamination/cleaning, (5) hoarding and (6) miscellaneous. However, there is no consensus on how all the individual symptoms should be organised into such factors (Pinto et al. 2009). In any case, this work has formed the basis of a rating scale: the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS; Rosario-Campos et al. 2006), see also 1.6.3.2.

### 1.4.6 OCD due to inflammation

From the 1990s and on, the notion that some OCD cases are the result of an autoimmune, neuro-inflammatory process in the brain, has attracted considerable interest, see further 1.5.5. To the extent that this at all is accepted as a diagnostic entity, some would view it as an entirely separate, neurological disorder, whilst others see this as an important subtype of the psychiatric disorder OCD, characterised by a distinct pathophysiology, and specific treatment options (Swedo et al. 1998 & 2012, Singer et al. 2012, Bejerot et al. 2013).

## 1.5 Aetiology and pathophysiology of OCD

### 1.5.1 Genetic and environmental factors

As in most other psychiatric disorders, there is evidence that both genetic and environmental factors contribute to the causation of OCD. A familial pattern has been evident, and twin studies, segregation analysis studies and genome-wide association studies (GWAS) have supported that there is a major contribution of additive genetic mechanisms (Nicolini et al. 2009, Stewart et al. 2013, Taylor 2013). This seems to be the case also concerning obsessive-compulsive symptoms in the population (Grabe et al. 2006), for which heritability based on single nucleotide polymorphisms (SNPs) was estimated at 14 % (den Braber et al. 2016). A study of Doberman Pinschers has extended the notion of a genetic aetiology of OCD-like phenomena to dogs (Tang et al. 2014).

However, epidemiological studies as well as twin studies support various environmental factors, of unique as well as shared character (Fontenelle & Hasler 2008, Cath et al. 2008). Age of onset and lifetime course both indicate the possibility that endocrine factors may be of importance, and there is support for a sexual dimorphism concerning symptoms and aetiology (Zohar et al. 1999, Lochner et al. 2004). Women, for instance,

have a considerably higher prevalence of OCD not only during the postpartum period but also when pregnant (Russell et al. 2013). Furthermore, several studies have shown that various types of antiandrogen treatment may ameliorate OCD, females as well as males (Eriksson 2007).

### 1.5.2 Brain imaging: morphology, circuits and function

A substantial amount of research data is at hand concerning what parts of the brain that may be involved in the mechanisms that give rise to obsessions and compulsions. There is evidence of increased activity in specific parts of the brain, forming an "OCD circuitry". This includes the orbitofrontal cortex, the caudate nucleus, globus pallidus and the medial dorsal nucleus of the thalamus (Hoehn-Saric et al. 1991, Schwartz et al. 1996, Saxena et al. 1998). An early positron emission tomography (PET) study (Baxter et al. 1992) was able to show normalisation of this overactive circuitry in improved OCD patients, irrespective of treatment (SSRI or behaviour therapy), supporting the clinical validity of these imaging findings. When patients specified for the different symptom dimensions (washing, checking and ordering) are studied with functional magnetic resonance imaging (fMRI), OCD seemed to be an etiologically heterogeneous disorder, with both overlapping and distinct neural correlates across these symptom dimensions (van den Heuvel et al. 2009).

### 1.5.3 Neurochemistry and psychopharmacology

#### 1.5.3.1 The serotonin hypotheses

##### 1.5.3.1.1 Clomipramine efficacy in OCD – unique at the time

For most psychiatric disorders, hypotheses regarding neurochemical mechanisms have materialised as a result of observations regarding treatment response to psychotropic drugs. This is the case, also in OCD. At an early stage, astute clinicians observed that the tricyclic antidepressant (TCA) clomipramine (also known as chlorimipramine or monochlorimipramine) seemed to have a specific anti-obsessive effect (Fernández Córdoba & López-Ibor Aliño 1967, Van Renynghe de Voxvrie 1968, Dickhaut & Galiatsatos 1968, Capstick 1971). At the time, however, little was known about any specific pharmacological properties of clomipramine. In pharmacological journals, however, Arvid Carlsson published the first studies to demonstrate one such property (Carlsson et al. 1969 a, b). Here it was shown that clomipramine differed from all other TCAs (as well as

all other drugs used in psychiatry at that time) by a considerably more potent inhibition of the neuronal transmembrane transport of serotonin (also referred to as 5-hydroxytryptamine (5-HT)), thereby plausibly potentiating this thitherto almost unknown transmitter in the brain.[3] At that time, however, clinicians could only speculate on the possible clinical impact of such serotonin potentiation.

Meanwhile, the hypothesis that depression (or a subgroup of depressions) was related to a deficiency of serotonin was put forward (Coppen 1967, Lapin & Oxenkrug 1969, van Praag et al. 1970, Bertilsson et al. 1974), why most psychiatric researchers focussed on depression when studying serotonin (Dencker et al. 1966, Åsberg et al. 1976, Åberg-Wistedt et al. 1982). Within the field of OCD, the first to present the idea of a serotonergic disturbance was probably Yaryura-Tobias and coworkers (1976 & 1977). In 1980, the first placebo-controlled evidence of clomipramine's efficacy in OCD was published (Marks et al. 1980, Montgomery 1980, Thorén et al. 1980 a). Undoubtedly, the most influential of these studies was the work from Stockholm, which was accompanied by a second article (Thorén et al. 1980 b), detailing information on cerebrospinal fluid (CSF) biochemistry and its alterations induced by the antidepressant treatment; see further 1.5.3.1.3. This work clearly directed the focus of neurochemical hypotheses to explain OCD pathophysiology towards the monoamine serotonin (Insel et al. 1985, Leonard et al. 1989, Goodman et al. 1990, Eriksson & Humble 1990), and, by doing this, also paved the way for more selective serotonergic drugs in the treatment of OCD. Meanwhile, the clinical efficacy of clomipramine in OCD was compellingly confirmed in two large, multi-centre, randomised controlled trials (RCTs) (DeVeaugh-Geiss et al. 1988, Clomipramine Collaborative Study Group 1991).

[3] It should be noted that serotonin had first been discovered in the gastric mucosa of rabbits by Vittorio Erspamer, who named the substance enteramine (Erspamer & Vialli 1937), and later in blood vessels. Betty Twarog (1954), when studying the nervous system of blue mussels, first revealed a potential role of serotonin as a neurotransmitter. In the 1960s, few believed that serotonin was of any importance within the human central nervous system (CNS).

#### 1.5.3.1.2 The SSRIs – heirs of clomipramine in OCD treatment

During the 1980s, the increasingly convincing evidence of the anti-obsessive efficacy of clomipramine inspired trials of SSRIs,[4] then under development as antidepressants, also in the treatment of OCD. The first reported positive case was treated with zimeldine[5] (Prasad 1983), followed by a successful case series (Kahn et al. 1984) and a small but positive controlled trial (Prasad et al. 1984). However, another small controlled trial with this compound disappointingly yielded negative results (Insel et al. 1985). In retrospect, this latter study constitutes a conspicuous exception from the ensuing positive results of almost all RCTs with SSRIs in OCD. Unfortunately, zimeldine was withdrawn from further trials due to immunological side effects, but further case reports or open trials followed with the other SSRIs: fluoxetine (Turner et al. 1985, Fontaine & Chouinard 1986), fluvoxamine (Price et al. 1987) and citalopram (Bejerot & Humble 1991).

Placebo controlled trials with positive results of an SSRI in OCD were first reported with fluvoxamine (Perse et al. 1987, Goodman et al. 1989 a). Eventually, all the presently used SSRIs were convincingly shown to be more effective than placebo in the treatment of OCD: fluoxetine (Montgomery et al. 1993, Tollefson et al. 1994), sertraline (Chouinard et al. 1990, Greist et al. 1995 a), paroxetine (Zohar & Judge 1996), citalopram (Montgomery et al. 2001) and escitalopram (Stein et al. 2007).

An interesting aspect of SRI/SSRI efficacy in OCD is the fastidiousness of this response. Depressive disorders by definition are responsive (to various extent) to all types of antidepressants, serotonergic as well as noradrenergic (Humble 2000, Dell'Osso et al. 2011), while most anxiety disorders tend to respond better to serotonergic antidepressants (Eriksson & Humble 1990, Ravindran & Stein 2010), e.g. SRIs and monoamine oxidase inhibitors (MAOIs), and, in addition, to the 5-$HT_{1A}$-modulator

[4] The acronym SSRI was seemingly introduced by pharmaceutical marketers around 1990. In the Medical Subject Headings (MeSH) system of Medline, these drugs are classified as serotonin uptake inhibitors (SUIs), and several researchers have tried to replace SSRI by the scientifically more consistent selective STI/SERTI (serotonin transporter inhibitor). Because of the ubiquitous recognition of SSRI, however, I have preferred to use this acronym throughout this thesis.

[5] This Swedish drug was originally named zimelidine, but the risk of confusion with cimetidine (then a common gastric ulcer medication) caused a change to zimeldine, shortly before its withdrawal from the market. The MeSH term in Medline is zimeldine.

buspirone. Nevertheless, in panic disorder, there is also evidence for efficacy of mainly noradrenergic antidepressants, such as imipramine, lofepramine and reboxetine (Zitrin et al. 1983, Fahy et al. 1992, Seedat et al. 2003). Since OCD respond poorly both to MAOIs and buspirone, this is the first and hitherto only psychiatric disorder where such a selective response to only one anti-depressive mechanism has been thoroughly documented.[6] Based on this, OCD seems remarkably suitable for elucidation of a specific mechanism of antidepressant drugs in non-depressive disorders. Actually, this extraordinary unanimity of almost all the studies of SRIs in OCD mainly suggests that serotonin is somehow involved in the physiological mechanism of anti-obsessive pharmacotherapy. Yet, it has also given rise to various hypotheses of a serotonergic dysfunction (including a deficiency of serotonin), purportedly central to the pathophysiology of OCD (Yaryura-Tobias et al. 1976, Thorén et al. 1980 b, Insel et al. 1985, Zohar & Insel 1987, Jenike et al. 1990, Eriksson & Humble 1990, Delgado & Moreno 1998, El Mansari & Blier 2006).

**1.5.3.1.3 Measurements of serotonin**

Previous researchers in the serotonin area (before 1990) had utilised several different methods to investigate inter-individual differences and treatment-induced changes related to serotonin. The most endorsed, as reflecting central nervous system (CNS) activity of the serotonergic system, was probably the measurement of 5-hydroxyindole-acetic acid (5-HIAA) in CSF (Bertilsson et al. 1972). However, since lumbar puncture is necessary in order to obtain the samples for this measure, both the invasiveness of this procedure and the requirements of skilled personnel preclude the use of CSF 5-HIAA as a biological marker in routine psychiatry. Because of this, the method has remained almost exclusively as a research tool. For this reason, several alternative methods, utilising peripheral blood, have been suggested to provide measures that somehow correlate with CNS serotonin activity.

Platelets are the containers of serotonin in peripheral blood and share the expression of several enzymes and receptors with the serotonergic neurons in the brain. They do not produce serotonin, but they take up serotonin (mainly produced in the enterochromaffin cells) from plasma

[6] It may turn out that premenstrual dysphoric disorder (PMDD) has a similar fastidiousness of its response to antidepressants, but to my knowledge, no one has presented trials with MAOIs in this disorder.

and store it in intracellular granules. The serotonin transport proteins of platelets and neurons are genetically identical (Lesch et al. 1993). Several methods of using radioactive ligands to measure binding to and kinetics of the serotonin transporter of platelets have been used, but due to methodological difficulties and inability to replicate findings (see e.g. Marcusson & Ross 1990) their validity is questioned, in spite of still being used, especially the [$^3$H]-paroxetine binding method (e.g. Marazziti et al. 1996).

Another type of peripheral measure is the amount of serotonin contained in platelets, which is expected to change during SRI treatment. Since the SRIs block the serotonin transporter, not only of the neurons but also of the platelets, the SRI-influenced platelets cannot take up serotonin from plasma. For the rest of their life cycle, their serotonin content will stay unchanged or diminish. The SRI will then prevent all new platelets, released from the bone marrow, from loading themselves with serotonin. The serotonin in plasma that has not been taken up by platelets will be degraded, mainly by monoamine oxidase (MAO), and excreted in urine as 5-HIAA. The serotonin levels can be measured in platelets, but this is technically very demanding due to the reactivity of the platelets, releasing their serotonin into plasma during sampling with little provocation. For the same reason, measurement of serotonin in platelet poor plasma is also a challenging procedure, sometimes with questionable validity (Yubero-Lahoz et al. 2014).

A method that circumvents the problems with reactive platelets is to measure serotonin in whole blood (WB-5HT). If the platelets release their serotonin load during the processing of the sample, their serotonin still remains in the homogenised blood. Since 95-99 % of the serotonin in whole blood is contained within the platelets, this will still be, in essence, a measure of platelet serotonin content. This method, WB-5HT, has previously been used to detect the effect of SRI treatment (Ross et al. 1976). WB-5HT has also consistently been found elevated in infantile autism (Cook & Leventhal 1996, Gabriele et al. 2014).

#### 1.5.3.1.4 But is there a serotonin deficiency in OCD?

During the first decades of research on the neurochemical pathophysiology of OCD, the unusually consistent findings concerning selective drug response granted the serotonergic hypotheses of OCD an unopposed position, and engendered a prolific research activity in the field. In spite of all the dedicated attempts to find evidence of a purported primary disturbance of the serotonergic system, disappointingly few unambiguous results

have emerged (Delgado & Moreno 1998, Aouizerate et al. 2005). However, at the time when we projected our study, several research groups had presented interesting findings in this field.

In their pioneering study, Thorén et al. (1980 b) showed that CSF 5-HIAA levels were significantly associated with clinical outcome in clomipramine-treated OCD patients. Higher baseline CSF 5-HIAA and a more pronounced decrease during treatment predicted better clinical response. Similar findings were made in a study of clomipramine treatment of childhood OCD (Flament et al. 1987), where the researchers used platelet serotonin content as an easily obtained model of the serotonergic system. Children with higher pre-treatment platelet 5-HT concentration (and more pronounced 5-HT/platelet decrease with treatment) improved more. Finally, one more recent study (Hanna et al. 1993) has replicated these findings, but using 5-HT in whole blood (WB–5-HT, see above) as an alternative serotonergic measure. This study also shows a positive correlation between 5-HT reduction and clinical improvement. On the other hand, a small study of CSF-5-HIAA by Insel et al. (1985) failed to replicate the original findings by Thorén et al. To our knowledge, based on Medline searches, no other attempts to replicate these correlations between dynamic changes of serotonergic measures and SRI anti-obsessive efficacy have been published.

Acute tryptophan depletion (ATD) is a commonly utilised method of testing the short-time effects of a significantly decreased serotonin availability in the brain, not only in experimental animals but also in humans. Many regard ATD as one of the most valid experiments for examining the effects of changing serotonin availability (Hood et al. 2005). Inspired by the SRI-treatment studies implying that OCD may represent a prototype among psychiatric disorders of serotonin deficiency, at least five research groups have examined the effects of ATD in OCD patients (Barr et al. 1994, Smeraldi et al. 1996, Berney et al. 2006, Külz et al. 2007, Corchs et al. 2015). After the first findings that, contrary to expectation, turned out negatively, different rationales were applied to motivate further experiments. However, no one was able to demonstrate even a tendency to accentuation of OCD symptoms during ATD.

With the advent of new imaging techniques, visualisation of serotonergic functions *in vivo* in humans has become achievable. By means of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) it is possible to label, quantify and describe the anatomical distribution of the serotonin transporter protein (SERT), as

well as several of the serotonin receptors. It is also possible to estimate the capacity of serotonin synthesising enzymes in localised parts of the brain by calculating the blood-to-brain clearance of α-[$^{11}$C]methyl-L-tryptophan, a radioactive synthetic analogue of tryptophan.

As summarised by several groups (Berney et al. 2011, Maron et al. 2012, Bandelow et al. 2016 a), the results of most PET/SPECT studies of serotonergic markers in OCD are disappointing if you expected to disclose a clear-cut deviation of serotonergic functions. The studies are either negative or inconsistent; e.g. imaging studies of SERT cerebral distribution show densities that are higher, lower or not different from controls. The only unopposed finding, hitherto, seems to be an elevated serotonin synthesis in the caudate nucleus and in parts of the temporal lobe, based on 21 OCD patients (Berney et al. 2011). Accordingly, these studies refute any deficiency or major dysfunction of the brain's serotonergic system, while the drug response data still support a crucial role of serotonin in the mechanism of action of the pharmacological treatment of OCD.

In this context, it should also be recalled that a considerable proportion of OCD patients do not respond to SRIs (Pallanti & Quercioli 2006), and that no consensus exists concerning which effects, downstream of the SRI-induced changes of serotonin availability that are involved in the clinical benefit (Delgado & Moreno 1998, McDougle et al. 1999). In spite of this, SRIs presently form the basis of OCD pharmacotherapy worldwide; see 1.6.5.

#### 1.5.3.2 Glutamate

Another neurotransmitter that has been shown to be of importance for OCD is glutamate. This was first hypothesised by Maria Carlsson (2000, 2001), based on theoretical reasoning related to the symptoms of OCD, the functions of the cortico-striato-thalamo-cortical circuitry and glutamate physiology. Since then, further support for the role of glutamate has accumulated (Wu et al. 2012, Pittenger 2015).

Several studies have documented some efficacy of glutamatergic drugs, but so far, none of these is widely used in clinical practice. There are promising trials with memantine (Feusner et al. 2009, Ghaleiha et al. 2013, Haghighi et al. 2013) and lamotrigine (Poyurovsky et al. 2010, Bruno et al. 2012, Hussain et al. 2015), while results with riluzole (Grant et al. 2014, Pittenger et al. 2015) and topiramate (Afshar et al. 2014) seem less impressive. On the other hand, the anaesthetic ketamine (a modulator of NMDA/AMPA receptors) has been tested, and found rapidly effective

in a small pilot trial (Rodriguez et al. 2013), when used in a similar way as when ketamine is used in the treatment of depression.

#### 1.5.3.3 Oxytocin and other peptides

Several researchers have put forward evidence that hypothalamic, especially neurohypophyseal peptides may be involved in OCD. Some data have supported a role for oxytocin and possibly also for vasopressin (Salzberg & Swedo 1992, Swedo et al. 1992, Leckman et al. 1994 b). One case report with positive result of intra-nasally delivered oxytocin against OCD (Ansseau 1987) spurred further interest in this peptide, but two randomised controlled trials of intranasal oxytocin treatment in OCD turned out negatively (den Boer & Westenberg 1992, Epperson et al. 1996). However, the bioavailability of intranasal oxytocin has been disputed.

Cerebrospinal fluid (CSF) levels of oxytocin have been measured in OCD patients, with elevated (Leckman et al. 1994 a) or normal (Altemus et al. 1999) findings. On the other hand, in subjects with autism spectrum disorders (ASD) a decreased function of oxytocin has been postulated (Insel et al. 1999, Dölen 2015). This is of interest, since a significant subgroup of OCD patients has autistic traits (Bejerot 2007), possibly confounding results in this field.

Several mechanisms connecting serotonin and oxytocin in the brain are reported in rodents (Jørgensen et al. 2003). It has also been shown in rats that plasma oxytocin increases with acute administration of the SSRI citalopram (Uvnäs-Moberg et al. 1999), while it was unchanged after 10 days of fluoxetine administration (Marar & Amico 1998). In patients with major depression, changes of oxytocin levels during various treatments have been reported (Ozsoy et al. 2009), but no correlation with clinical response was found.

To our knowledge, there was only one study prior to our (paper IV), that investigated oxytocin changes during SRI treatment of OCD patients. In this study, clomipramine treatment for a mean of 19 months increased cerebrospinal fluid (CSF) levels of oxytocin by 11 % in 17 paediatric OCD subjects (Altemus et al. 1994). Unfortunately, only the patients that had responded to treatment were analysed, hence the study could not reliably relate biochemical changes to clinical response. In addition, since no placebo treated group was included, conclusions from this study on the pharmacological effects of SRIs on the oxytocin system should be viewed with caution.

### 1.5.4 Neuro-inflammation: autoimmune reactions, infections

A widespread trend of research on psychiatric aetiology is an increasing awareness of immunological, inflammatory mechanisms.

In 1995, Susan Swedo and her collaborators proposed a new putative subtype of OCD (Allen et al. 1995). They originally conceptualised this as a specific autoimmune reaction connected to *Streptococcus* infection, akin to rheumatic fever, hence labelled "Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection" (PANDAS). A few years later they were able to present 50 cases (Swedo et al. 1998), however, the validity of this disease mechanism has been questioned. Recently, however, more evidence has become available, supporting an autoimmune mechanism and suggesting a slightly differently delineated clinical entity: Paediatric Acute-onset Neuropsychiatric Syndrome (PANS), which should be considered in cases of rapidly emerging obsessions, compulsions, tics or anorexia accompanied with separation anxiety, personality change, motor impairment and/or urinary frequency among children (Swedo et al. 2012). An alternative formulation to delineate this still enigmatic group of patients is Childhood Acute Neuropsychiatric Symptoms (CANS), suggested by Singer et al. (2012). For treatment, antibiotics and/or intravenous immunoglobulin may apply, as recently reviewed (Bejerot et al. 2013).

A different type of infectious aetiology has been suggested: neurotropic infection with *Toxoplasma gondii*. This parasitic protozoan, sharing its life cycle between cats and one other host (e.g. rodents or humans), is ubiquitously infecting a significant proportion of the human population. Many studies have supported a connection between this infection and schizophrenia, but now also OCD has been studied. In a meta-analysis of these studies (Sutterland et al. 2015) an elevated rate of *Toxoplasma* seropositivity compared to controls for schizophrenia was confirmed, but OCD attained even higher seropositivity rate, with an odds ratio of 3.4. The included studies on OCD were small, however, and more studies are necessary.

## 1.6 Clinical management of OCD and its obstacles

### 1.6.1 Patient identification and recognition

In clinical settings of primary care as well as psychiatry, OCD often appears to be a relatively uncommon target for interventions (Fireman et al. 2001). This may be surprising, given the epidemiological evidence that OCD is a relatively common psychiatric condition in the population,

which often leads to a chronic course, and that it rather often entails an advanced degree of functional disability.

There may be several reasons for this under-recognition:

- The patients themselves are secretive about their ailment and reluctant to seek help. They (and also their kin) may lack the information that their "weakness" is part of a generally recognised disorder. If they believe that the problems are just related to an eccentric ingredient of their personality, they may have little reason to envisage treatment possibilities. Shame or embarrassment due to the offending or silly content of the obsessions or due to their inability to master the compulsions may also contribute to the concealment (Bejerot 1992, Weingarden & Renshaw 2015).
- Even if the persons are aware of the psychiatric nature of the problem, they may not be aware of the availability of successful treatment alternatives. They may also fear feeling stigmatised by seeking help from psychiatry.
- Against this background, cases with longstanding OCD may commonly first seek help when other, secondary or co-morbid health problems occur, e.g. depression and anxiety (Torres et al. 2007) or dermatological problems (Fineberg et al. 2003).
- Caregivers may not uncover the primacy of OCD, when patients come to their attention for other reasons.
- Caregivers may also lack the necessary competence for identification of OCD and/or for providing specific treatment of the disorder.

One way of remediating this problem is to disseminate publicly information about OCD, something that in Sweden is successfully operated by a patient organisation for OCD, "Svenska OCD-förbundet Ananke". But in order to mitigate the caregiver's problems, this may not be enough. In a recent survey where clinical vignettes were presented to primary care physicians in New York, 50.5 % of the OCD cases were misdiagnosed by the physicians and recommended inappropriate treatments (Glazier et al. 2015), demonstrating the need for education of the medical profession. Among OCD patients treated by psychiatrists in the USA, 47 % received evidence-based treatment (Blanco et al. 2006). In Sweden, 61 % of medi-

cated OCD patients receive adequately dosed SRI treatment (Isomura et al. 2016). It should be noted, however, that this was a registry study, reporting only on cases identified as OCD within health care, representing a small proportion of the epidemiologically predicted prevalence. Notably, it has been shown in Germany that even in psychiatric specialist care, only 28 % of patients with OCD were recognised as such by their treating clinician (Wahl et al. 2010). To some extent, this may well be the result of the OCD patients' reluctance to disclose their symptoms. Furthermore, the higher rates of OCD in epidemiological studies may represent transient or less severe cases, not requiring treatment. Regardless, it seems clear that a large proportion of the OCD cases in the community go unrecognized, and that health care professionals need to improve their ability to identify OCD.

### 1.6.2 Rating scales for use in psychiatric disorders

A commonly utilised method of facilitating clinical recognition and assessment is to provide different types of rating scales or related assessment instruments. Rating scales for psychiatric disorders may be generally classified as either *diagnostic scales* or *severity scales*. The diagnostic scales may be used as broad screening instruments, when there is insufficient knowledge what to search for, or more specific instruments, corroborating an emerging suggestion of the type of pathology that is present. In routine psychiatric praxis, comprehensive diagnostic screening instruments like the "Schedules for clinical assessment in neuropsychiatry" (SCAN, Wing et al. 1990) or the "Structured clinical interview for DSM disorders" (SCID, First et al. 1996) are rarely utilised. At the most, the "Mini-international neuropsychiatric interview" (MINI, Sheehan et al. 1998) may be used. In research, however, relevant parts of these comprehensive diagnostic scales are often applied.

The severity scales are used when the type of pathology that should be in focus has been settled, and are often specific for a certain diagnosis. For example, one of the most common severity scales is the Montgomery-Åsberg Depression Rating Scale (MADRS, Montgomery & Åsberg 1979). In the case of OCD then, the overall severity of the disorder, the severity of the obsessions, the compulsions or the impairment, or to what extent the quality of life is decreased, may all be the focus of the severity rating. See further 1.6.3.

Another type of classification of rating instruments is based on by whom it is performed. The most common options are *clinician rating*

*scales* and *self-rating scales*. Psychiatric clinician ratings are usually performed as a structured interview with the patient, covering a number of items considered relevant for the purpose. In such interviews, the clinician elicits statements from the patient concerning the presence or the severity of their symptoms. For specific purposes, pure observer scales have been developed, e.g. the CORE system (Parker & Hadzi-Pavlovic 1996) for the assessment of melancholic depression with special focus on psychomotor retardation. In this type of assessment, the clinician observes specified variables during a conversation with the patient, whose statements are not as important as the way in which the statements are made.

Self-rating scales are usually presented in the form of questionnaires or checklists, in which the patient ticks boxes for the various response alternatives. This could also be made by use of computers or on the internet. Other rating options are spouse rating, caretaker rating or teacher rating. These are mainly used when assessing children or individuals with intellectual disability or dementia.

### 1.6.3 Specific rating scales for OCD

#### 1.6.3.1 Early OCD scales

In the case of OCD, there has been a considerable increase of alternative scales during the last decades. Before 1980, however, few useful scales were at hand. Exceptions were the Leyton Obsessional Inventory (Cooper 1970) and the Maudsley Obsessive-Compulsive Inventory (MOCI) (Hodgson & Rachman 1977), both mainly used as self-rating questionnaires. Thorén and his group in Stockholm (1980 a) empirically selected eight OCD-relevant items, as a subscale out of the 65 items included in the Comprehensive Psychopathological Rating Scale (CPRS) item pool (Åsberg et al. 1978). However, only two or three of the items were OCD-specific; the rest are similarly included in subscales for depression or anxiety. When the National Institute of Mental Health, USA, were planning to launch their research program on OCD, Insel & Murphy (1981) reviewed the problems with available scales. They then developed the National Institute of Mental Health Global Obsessive Compulsive Scale (NIMH-GOCS) (Insel et al. 1983), a 1 item, 15-graded scale, which is still in use and was included in our treatment study.

#### 1.6.3.2 The Y-BOCS and its derivatives

A major breakthrough was the publication of the "Yale-Brown obsessive compulsive scale" (Y-BOCS) (Goodman et al. 1989 b, c). In short time, it came to be regarded as the gold standard for rating the severity of OCD, in research as well as clinical settings. We used this scale in a Swedish version throughout the research included in the present thesis.[7] The Y-BOCS was originally introduced and applied in the evaluation of symptom severity and treatment response in adult patients with a diagnosis of OCD. A very similar version for children (CY-BOCS) was introduced in 1997 (Scahill et al. 2006). Both versions have been widely used in research and in clinical settings (Leckman et al. 1997, Nikolajsen et al. 2011). However, it was noted that the severity rating of the Y-BOCS could be improved by including assessments of obsessive-compulsive free intervals and extent of avoidance. A second edition of the Y-BOCS (Y-BOCS-II) included these improvements (Storch et al. 2010 a, b).

Both Y-BOCS versions, as well as the CY-BOCS, have two parts: the first part consists of an extensive symptom checklist of 54 items in the Y-BOCS and more than 60 items in the CY-BOCS; the items are grouped into 13 categories, 7 for obsessions and 6 for compulsions. The second part is a separate clinician-rated scale measuring symptom severity on 10 items that are summed up to a severity score, ranging between 0 and 40. An even more comprehensive measuring tool was developed in the 88 item Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS), measuring severity within six independent symptom dimensions (Aggression, Sexual/religious, Symmetry, Contamination, Hoarding, and Miscellaneous) (Rosario-Campo 2006, Pertusa et al. 2012). The Y-BOCS and the DY-BOCS were both developed as comprehensive clinician rating instruments for OCD, but rather soon, a self-rated version of Y-BOCS became available (Baer 1991, Rosenfeld 1992). There is a good agreement between the self-rated instrument and the original Y-BOCS (Steketee et al. 1996), however less for obsessions than for compulsions (Federici et al. 2010).

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[7] The Swedish translation of Y-BOCS was made by Susanne Bejerot and Mats Humble. Our Swedish text was tested at our clinic and, after some adjustments, back-translated into English. The result of this was compared to the original, and since the correspondence was deemed adequate, this translation was launched. It has been made freely available on the internet at:
www1.psykiatristod.se/Global/Psykiatristod/Bilagor/angestsyndrom/Y-BOCS.pdf

#### 1.6.3.3 The need of alternative scales

In the 1990s, the Y-BOCS was the obvious alternative for rating OCD. It is well suited for research, but in clinical psychiatry, the time required to complete a Y-BOCS rating is rarely available. In spite of the improvements in Y-BOCS-II, one unnecessarily cumbersome feature of the scale remains, namely the separate recording and rating of the obsessions and compulsions even if they were closely related (e.g. contamination and washing), both in the checklist and in the severity ratings. For the patient as well as for the clinician, this is both counter-intuitive and time-consuming.

Accordingly a more succinct (shorter and easier for the everyday patient to grasp), but still psychometrically valid and reliable rating instrument for OCD would be clinically useful. Other research groups have presented new rating scales for OCD (see 6.1.1), but all have their shortcomings, and there is still no consensus on alternatives to the Y-BOCS.

### 1.6.4 Psychological OCD treatment – cognitive behavioural therapy[8]

During the first half of the 20th century, many psychoanalysts, including Sigmund Freud, attempted treatment of OCD, usually with disappointing results (Jenike 1993, Esman 2001). When behavioural therapists applied novel, OCD-specific methods, however, OCD patients clearly benefitted. The most successful technique for compulsions has turned out to be real life exposure with self-imposed response prevention (Marks et al. 1975).

Later, specific methods for obsessions, inspired by cognitive therapy, were successfully applied to the treatment of OCD patients (Rachman 1997, Salkovskis 1999). Thus, some specific methods classified under the umbrella designation cognitive behavioural therapy (CBT) are by now well documented as effective in OCD treatment. It should be noted, however, that these techniques are relatively demanding, that more severe OCD cases usually require very experienced therapists and that relapses are common (Feusner et al. 2015). Furthermore, a considerable proportion of OCD patients is reluctant to undertake CBT; in a recent study, 46 % refused even to start with CBT (Santana et al. 2013).

In Sweden, the National Board of Health and Welfare recommends CBT as first hand treatment for OCD (Socialstyrelsen 2010). Considering the current research literature, this is well supported by the evidence, pro-

[8] While acknowledging the major importance of psychological treatment in OCD, the description here is summarised, since psychological treatment has not been the focus of the research included in this thesis.

vided that the specific, primarily behavioural but also cognitive, techniques, evaluated for OCD treatment, are utilised. However, the availability of therapists, trained in these techniques, is a limiting factor (O'Neill & Feusner 2015), and it is important that psychopharmacological treatment is available for the cases that cannot be successfully treated with CBT.

### 1.6.5 Pharmacotherapy for OCD – present recommendations

International guidelines for pharmacological treatment of OCD has repeatedly been disseminated by the World Federation of Societies of Biological Psychiatry (WFSBP), most recently in 2008 (Bandelow et al. 2008). According to them, there is full evidence from controlled studies for the efficacy of the SSRIs escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; and also for the TCA clomipramine. However, no other drug of any other category attained this grade of evidence. They also clearly state that there is no evidence for superior efficacy of clomipramine or any of the SSRIs, when compared to the others. Considering the significantly higher rate of adverse effects with clomipramine, WFSBP recommends any of the mentioned SSRIs as first-line treatment, with clomipramine as a second-line alternative.

The Swedish national guidelines for treatment of OCD (Socialstyrelsen 2010), ranks the pharmacological treatment alternatives in adult patients with clomipramine as first choice and SSRI as second; however, the rationale for preferring clomipramine to SSRI is not evident from their guideline text.

More recently, guidelines of the British Association for Psychopharmacology (Baldwin et al. 2014) and the Anxiety Disorders Association of Canada (Katzman et al. 2014) have been released. In essence, they reiterate the recommendations of WFSBP, but their recommendations how to deal with nonresponse to SRIs are more elaborated, suggesting not only combined treatment with antipsychotic agents but also some novel alternatives for pharmacological augmentation of SRI treatment, e.g. addition of the glutamatergic modulator memantine or of the 5-$HT_3$ antagonist ondansetron.

Common to all guidelines on OCD treatment is the concept that these patients may need considerably higher dosage of clomipramine or SSRIs (compared to patients with depressive disorder) and extended time on treatment in order to respond to SRI pharmacotherapy.

### 1.6.6 Other OCD treatments

There is a general consensus that electroconvulsive therapy (ECT) is not generally indicated in OCD treatment. However, in a systematic review of the available literature, Fontenelle et al. (2015) found that out of 279 ECT-treated OCD cases, 60.4 % were reported as responders. However, these were uncontrolled reports, there was incomplete information on the nature of these patients and publication bias could not be excluded. Due to this, the authors made no conclusions concerning treatment recommendations.

As a development of previous use of irreversible neurosurgery methods for OCD treatment, deep brain stimulation (DBS) is now under evaluation for OCD treatment. For recent reviews, see Blomstedt et al. (2013) and Kisely et al. (2014). The effects of these invasive methods are of major interest for the elucidation of the neuroanatomical biology of OCD (see 1.5.2). On the other hand, DBS is not yet ripe for clinical use outside research programs, one reason being that the evidence for long-term efficacy is still wanting. Moreover, adverse effects from neurosurgical procedures for psychiatric disorders have been conspicuously underreported since the era of lobotomy (Bejerot 2003).

### 1.6.7 Side effects and their possible utility

#### 1.6.7.1. Side effects versus adverse effects

Pharmacotherapy of OCD, per definition, has anti-obsessive efficacy. Other effects can be seen as *side effects*. Since most drugs used in OCD belong to the SRI antidepressant class, efficacy against depressive symptoms, if present, may also be expected. In most cases, this would represent a most welcome side effect, as would anxiolytic and sleep-improving effects. If the patient has a comorbid bipolar disorder, however, antidepressant effects could become problematic, possibly causing a switch into mania (Berk et al. 1996). A manic switch induced by SRI treatment, then, should be classified as an *adverse effect*, i.e. the subgroup of side effects that are undesirable.

The ambiguity of these definitions can be further exemplified by SRI-induced sexual dysfunction. These side effects are widely acknowledged and publicised as one of the major drawbacks of SSRI treatment, thus clearly an adverse effect. Yet, in the case of males suffering from premature ejaculation (*ejaculatio præcox*), the delay of orgasm/ejaculation typically induced by SSRIs has become a major therapeutic strategy

(Castiglione et al. 2015). There is even a newer SSRI compound, dapoxetine, which was specifically developed and is now marketed for this purpose (Pryor et al. 2006). The rather modest results of this marketing are probably explained by the competing availability of inexpensive paroxetine, which is also well documented for this indication.

#### 1.6.7.2 Potential pathophysiological significance of side effects

Another line of investigation is whether side effects of pharmacotherapy have any relation to the mechanisms leading to treatment response. In such research it is important to consider that if a side effect is commonly occurring, it may simply constitute a clinical marker of compliance, i.e. that the patient has been taking the drug as prescribed. In that case, the side effect, supposedly, should correlate with the measured concentration of the drug, which in turn would correlate with the clinical response.

However, if a group of seemingly similar patients are dissimilarly drug responsive in spite of comparable drug concentrations (which is often the case in psychopharmacology), then the differential drug response may depend on hitherto undefined inter-individual differences, e.g. concerning genetic polymorphism, neuroendocrine regulation, neuroanatomical wiring, etc.; likely to constitute so called *endophenotypes*.[9] In that case, these inter-individual differences may also be linked to differential susceptibility to certain side effects by similar mechanisms as they are linked to drug response. Accordingly, side effects may not only inform on the patients' compliance, but possibly also represent a link to the putative "drug response endophenotype", which then would be easily discernible in clinical practice by carefully observing the side effects. By using data from large multi-centre trials of clomipramine and fluoxetine in OCD, Deborah Ackerman and co-workers could show that some side effects, initial nervousness and sexual complaints, were associated with later anti-obsessive response to both of these drugs (Ackerman et al. 1999). The authors also commented that the initial nervousness or excitement, since it is easy to detect and subsides after the first few weeks, could be clinically useful if the patient needs encouragement to continue the treatment. However, they

[9] Endophenotype is usually defined as a heritable trait (or biomarker), specifically associated with a disorder and forming a "hidden" link between the overt symptoms and signs of this disorder (the phenotype) and its genetic basis. When implementing this concept, the aim is usually to facilitate the identification of aetiologically more homogeneous groups for resolving a hypothetical genetic causation (Beauchaine 2009).

were less enthusiastic about similar utility of the sexual side effects, which tend to persist and even may cause treatment discontinuation, eventually. Nevertheless, these findings reinforced our interest in sexual side effects of SRIs, which is the focus of paper V.

### 1.6.8 Treatment response and treatment resistance

#### 1.6.8.1 Treatment response definitions

According to the available literature, a majority of OCD patients will eventually have a meaningful improvement from specific anti-obsessive treatment. However, it has been unexpectedly difficult for the research community to agree on how to define response to anti-obsessive treatments. Prior to the Y-BOCS, individual researchers invented their own methods (e.g. Capstick 1971, Thorén et al. 1980 a, Insel et al. 1983), and the dichotomization between responders and non-responders was not seen as in need of definition.

Although the Y-BOCS scale has now been administered in most treatment trials for decades; until recently, no clear definition of treatment response, when using this scale, has been accepted by the research community. In most of the pharmacological OCD treatment studies, the Clinical Global Impression-Improvement scale (CGI-I, Guy 1976) has been used in addition to the Y-BOCS. Some studies have used "very much improved" or "much improved" (i.e. score 1 or 2) on the CGI-I scale as response definition. Others have used 25 % decrease of Y-BOCS scores or 35 % decrease of Y-BOCS scores. Finally, several studies have used a combination of 1 or 2 on the CGI-I *and* 25 % decrease of Y-BOCS scores as definition of response to treatment (see e.g. Fineberg et al. 2012).

However, in 2016, David Mataix-Cols and co-workers presented the results from a large international consensus study (web-based "Delphi survey"), including 326 OCD researchers. Here, the definition of response, which was ultimately agreed on, was at least 35% decrease in the Y-BOCS and very much improved or much improved on the CGI-I scale (Mataix-Cols et al. 2016).

#### 1.6.8.2 Non-response and treatment resistance

With any of the above response criteria, a considerable proportion of the patients, by definition, will be non-responders. A patient with repeated non-response to both CBT and SRI treatment will eventually be labelled treatment resistant or treatment refractory (Pallanti & Quercioli 2006).

There are a number of further interventions that have been evaluated and that may be worth trying in the treatment of such patients; see e.g. 1.6.5 and 1.6.6.

### 1.6.9 Problems in current management and understanding of OCD

#### 1.6.9.1 Under-recognition of OCD in clinical practice

As already discussed in 1.6.1, for many reasons, persons with OCD are reluctant to seek help and, if they do so, their OCD is frequently missed. Usually, the clinician implements an open interview, covering various aspects of psychopathology, and then, based on general impressions from this first probing, focusses on certain areas that are believed to encompass the most relevant psychopathology. If a suspicion of obsessions or compulsions arises, then a more detailed questioning on this would ensue. In this situation, a user-friendly, succinct rating scale with listed items specifically identifying obsessive-compulsive symptoms could be very helpful. Ideally, the scale should also be useful for reliably assessing OCD severity and be possible to use as a self-rating screening instrument. Unfortunately, a psychometrically sound instrument, tested in large psychiatric populations, that fulfils these requirements has been lacking.

#### 1.6.9.2 Response prediction

In psychiatric treatments, better methods of objectively guiding the clinician how to proceed with the treatment would be valuable. In OCD pharmacotherapy, about 50 % of the patients respond to SRIs, according to controlled trials (Greist et al. 1995 b, Kobak et al. 1998, Fineberg et al. 2012). Treatment response is slow, however, and it is recommended to pursue an unsuccessful drug treatment for at least ten weeks before it is discarded (Greist & Jefferson 1998). The OCD patients are often afraid of possible harms connected to the medication and some will initiate complicated rituals of medication administration that may obstruct the treatment completely. Indeed, some patients, in order to comply with treatment, need such extended encouragement, that treatment becomes unfeasible.

For these and other reasons, response predictors for anti-obsessive SRI treatment may be of considerable clinical usefulness. For instance, an initial measurement that predicts the likelihood that the patient will respond to a particular treatment would be very useful in the clinic. Various biochemical measures have been suggested to reflect psychiatric disorders, both as trait markers and as state markers, e.g. the dexamethasone sup-

pression test (Carroll 1982) or the CSF concentration of 5-HIAA (Bertilsson et al. 1972, Åsberg et al. 1976, Träskman et al. 1981). Since the most commonly recommended long term drug treatments in OCD are supposed to work through modulation of the serotonergic system and are also used as antidepressants, markers related to serotonin have been tested with these drugs, however, mainly in the treatment of depressive disorders. For different reasons, none of these has won reasonable acclaim in the treatment of either depression or anxiety disorders.

In the case of OCD, at the time of our study, only a couple of research groups had tried to identify various types of biochemical response predictors. A pioneering study (Thorén et al. 1980 b) showed that the decrease in cerebrospinal fluid (CSF) levels of 5-hydroxyindole-acetic acid (5-HIAA, the main metabolite of 5-HT) correlated significantly with clinical outcome in clomipramine treated OCD patients. Patients with a higher initial CSF 5-HIAA level and a more pronounced decrease during treatment improved more. Similar findings were made in a study of clomipramine treatment of childhood OCD (Flament et al. 1987). In this study, children with higher pre-treatment platelet 5-HT concentration (and more pronounced 5-HT/platelet decrease with treatment) improved more. To our knowledge, these findings have not been replicated. A possible reason for this may be that neither measurements of CSF-5-HIAA nor platelet 5-HT concentration are simple methods, suited for everyday clinical practice.

Many researchers have used common clinical variables in order to find useful response predictors. In the large RCT trials, variables that are statistically linked to response tend to be either absent (DeVeaugh-Geiss et al. 1989) or intuitively predictable, such as initial severity of OCD, duration of OCD and age of onset. The more severe the disorder, the longer the duration, the earlier the onset and the more treatments attempted, the poorer is the response to treatment (Stein et al. 2001, Skoog & Skoog 1999). A family history of OCD may predict good treatment response, while poor insight predicts poor response (Erzegovesi et al. 2001). In a recent study of childhood onset OCD, poor visuospatial and fine motor skills predicted persistence of OCD into adulthood (Bloch et al. 2011).

#### 1.6.9.3 Adverse effect burden

The adverse effects of SRI treatment are related to a number of parameters, e.g. the pharmacokinetics and pharmacodynamics of the individual drug, the dose of the drug (the effects of clomipramine are more clearly

dose related than those of the SSRIs), but also related to the phase of treatment. Several adverse effects are most pronounced or most common during the initiation of treatment and then subside. Since OCD often has a chronic course and relapses after discontinuing SRI treatment are common, patients that have responded favourably often choose to continue with long-term treatment. In this situation, adverse effects that remain during long-term treatment will be of major importance. In this respect, clomipramine has well-known drawbacks as compared to the SSRIs (Bandelow et al. 2008, Fineberg et al. 2012). The anticholinergic effect due to muscarinic antagonism may cause chronic xerostomia and constipation, with increased risk for caries and diverticulosis. In the elderly, anticholinergic drugs increase the risk of cognitive impairment and delirious states. High concentrations of clomipramine may also increase the risk for epileptic seizures and cardiac arrhythmias. The SSRIs benefit from negligible muscarinic antagonism, why the easily observable anticholinergic effects rarely cause problems. Accordingly, they are more suitable for long-term treatment. On the other hand, pharmaco-epidemiological studies have unveiled some other effects of long-term SSRI treatment, probably related to their serotonergic effects. Serotonergic influence on bone metabolism may cause a discrete but significant decrease of bone mineral density and increased risk of fractures, and this effect is more pronounced with SSRIs compared to TCAs (Rabenda et al. 2013).

#### 1.6.9.4 Biochemical targets of medications

The history of psychopharmacology tells us that in order to discover clinically useful effects of psychotropic drugs, awareness of the neurochemical mechanism of the drug is superfluous, while clinical observation is indispensable (Ban 2006). The clomipramine – OCD story is a good example of this. Already in the 1960s, sensible clinicians first described the anti-obsessive effect of clomipramine (Fernández Córdoba & López-Ibor Aliño 1967, Van Renynghe de Voxvrie 1968), but almost two decades elapsed

while waiting for the crucial mechanism to be unanimously established.[10] However, when attempting to improve the utility of an established type of pharmacotherapy (increase the efficacy, decrease the adverse effects, etc.), this process usually gains much from information on the details of the mechanisms involved, thereby enabling a search for alternatives achieving the same goal.

It is therefore somewhat disconcerting that no real answer has yet been provided to the question of why SRIs are effective in OCD, apart from the circularly defined fact that they inhibit the transmembrane transport of serotonin. Which are the further neurochemical/neurobiological events, beyond the altered chemical milieu of the serotonergic synapses that mediate the anti-obsessive effect? This has been a focus in paper IV and will be further discussed in 6.2 and 6.5.

Our work with this intriguing disorder started in the late 1980s. The diagnostic boundaries of OCD were somewhat blurred, but the serotonin hypothesis had just been to some extent established. In her research, Susanne Bejerot focussed on the diagnostic issues, such as comorbidity with personality disorders and autism spectrum disorder. My part was to focus on the pharmacological questions, including the possibility to guide the clinical treatment by means of biological markers. Finally, we both realised that a more practicable rating scale would be essential, in order to extend the promising treatment alternatives to those that would benefit most.

[10] To some extent, this seems to have been a matter of transatlantic rivalry. Clomipramine was a European drug, launched by the Swiss company Geigy in 1966. The FDA did not approve clomipramine until 1990, and before this, it was not marketed in the USA. The proponents of the serotonin hypothesis were mainly Europeans (see 1.5.3.1), while US researchers focussed more on the catecholamines (e.g. Schildkraut et al. 1978). The mental shift regarding serotonin in the USA actually seems to coincide with the years when the American company Eli Lilly & Co were developing fluoxetine, the first marketed SRI in the USA, launched in 1988 as Prozac.

# 2 Aims

## 2.1 General aims

Our primary objective was to develop scientifically based methods that could improve the clinical management of OCD, especially the pharmacotherapy. To that end, we pursued several paths. Common to all was our ambition to find uncomplicated, inexpensive methods that could realistically be implemented in clinical settings.

A secondary aim was to contribute, potentially, to the ongoing disentanglement of the neurochemical pathophysiology of OCD, and of the biochemical mechanisms involved when SRIs exert their anti-obsessive effects as well as their side effects.

More specifically, we stated our aims as follows.

## 2.2 Development of a clinically useful rating instrument

We aimed to develop and test in clinical practice a new rating scale for assessment of OCD, based on the Y-BOCS, with the following properties:

- simple and efficient to use for self-rating as well as for clinician-rating
- useful for identification of a range of common OCD symptoms, covering the principal symptom themes (thereby assisting in the diagnostic process)
- reliably producing severity ratings, specific for OCD and related disorders
- avoiding some of the draw-backs that had been identified with the Y-BOCS

The unavoidable decrease of comprehensiveness would be acceptable, as long as the new scale could identify OCD cases among mixed psychiatric patients and reliably rate their severity. Therefore, in the clinical testing of our simplification of the Y-BOCS (the BOCS) we aimed to demonstrate that our novel scale still retains a coverage of the several symptom theme "dimensions", highlighted in recent research (see 1.4.5). Accordingly, our hypothesis was that, in a principal component factor analysis of symptom checklist ratings received from a large and diverse clinical population, factors would emerge that by and large resemble those obtained in studies with the Y-BOCS. A second hypothesis was that patients diagnosed with

OCD by established methods would have significantly higher scores on both the symptom checklist and the severity rating parts of the BOCS scale, as compared to groups of various psychiatric patients with other diagnoses. Furthermore, we wanted to test whether the scores on BOCS could discriminate OCD patients from non-OCD psychiatric patients with a satisfactory sensitivity and specificity.

## 2.3 Treatment response prediction with biochemical measures

We aimed to test in a clinical sample of OCD patients whether easily obtainable biochemical samples (e.g. related to serotonin and oxytocin), taken before treatment or early in SRI treatment, may predict the subsequent anti-obsessive response, and whether serotonergic side effects (change of sexual functions) may contribute to this prediction.

In paper II-III, our primary hypothesis was that by repeated measurements of serotonin in whole blood (WB-5HT), we would be able to identify a time-point (in relation to SRI therapy start), where the WB-5HT levels could predict the clinical response. We would then use baseline WB-5HT and the percentage decrease of WB-5HT relative to baseline, and compare these values with the later anti-obsessive outcome (decrease of Y-BOCS scores, after 12 weeks of treatment or at endpoint). We expected that a more pronounced decrease of WB-5HT would correspond to a better anti-obsessive response, thus replicating previous work that predicted outcome in OCD treatment (Flament et al. 1987, Thorén et al. 1980 b), but with a considerably simpler and clinically feasible methodology. On the other hand, we did not expect any change of WB-5HT in the placebo treated patients, why the correlation to response was only likely to appear among the SRI treated patients (clomipramine or paroxetine).

Similarly, in paper IV-V, our general hypothesis was that plasma oxytocin would be somehow related with OCD severity, anti-obsessive response and/or sexual side effects. Because no previous studies of this type were available, these studies were essentially explorative in nature. However, we were able to test the following hypotheses: 1. to confirm or refute the previously disputed positive correlation between baseline oxytocin levels and the individual's severity of OCD (Leckman et al. 1994 a, Altemus et al. 1999), 2. to test whether an increase of oxytocin at some time point is positively related to anti-obsessive response among SRI-treated subjects, and, 3. to test whether SRI induced sexual dysfunction is linked to a decrease of oxytocin levels during treatment.

## 2.4 Clues to SRI mechanisms and OCD pathophysiology

Finally, we aimed to utilise the acquired data in an attempt to elucidate further the biochemical mechanisms involved in the anti-obsessive effect and the sexual side effects of SRIs, with possible implications for the neuroendocrine pathophysiology of OCD.

# 3 Methods

## 3.1 Patients

### 3.1.1 Subjects for paper I

During the initial development of the BOCS, a group of 61 OCD patients were included, essentially the same cohort as those included in a study on personality and smoking in OCD (Bejerot et al. 2000).

For the subsequent psychometric testing, the sample consisted of 402 psychiatric outpatients (from 18 to 82 years of age) recruited from several different clinical and non-clinical settings in Sweden. Ninety-four out of these patients had a primary diagnosis of OCD, 82 had ASD, 157 had ADHD and 69 constituted a mixed psychiatric group with other psychiatric diagnoses e.g. depression or eating disorder. Data for some patients were drawn from other studies (Ståhlberg et al. 2004, Mörtberg et al. 2007, Rydén & Bejerot 2008, Bejerot et al. 2010), while others were specifically recruited for this study.

A subgroup consisting of 12 OCD outpatients was included from a cognitive behavioural therapy (CBT) treatment program at a psychiatric outpatient unit in Stockholm. These patients were assessed with the NIMH-GOCS (Insel et al. 1983, see 1.6.3.1), in addition to self-assessment with BOCS prior and post treatment. They received weekly treatment with a mean of 16 treatment sessions.

Patients with primary diagnoses of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) were consecutive referrals either to St. Göran's hospital in Stockholm, or to the Gothenburg Neuropsychiatric Genetic Project. If the SCID I interview (First et al. 1996) suggested any sign of obsessions or compulsions they were further assessed with the BOCS.

A mixed psychiatric group consisted of patients with primary diagnoses of (non-OCD) anxiety disorders, tic disorders, depression, eating disorders, and personality disorders. They were recruited through the specialised outpatient clinic at St. Göran's hospital, the Gothenburg Neuropsychiatric Genetic Project or for a research project on social anxiety disorder (recruited by advertisement for a CBT study on social anxiety disorder).

### 3.1.2 Common cohort for paper II-V

The cohort of OCD patients that were used for our biochemical studies were originally recruited for an international multi-centre clinical trial, aimed at establishing the efficacy of paroxetine (PXT) in the treatment of OCD.[11] The trial was planned as a three-armed, parallel-groups, placebo and reference controlled, double-blind, 12 weeks' trial. As reference drug, clomipramine (CMI) was used. In the following, our Danderyd (Stockholm county) based part of this multi-centre trial will be referred to as PXOS (the paroxetine obsessive-compulsive study). The merged results at the multi-centre level were published in the British Journal of Psychiatry (Zohar & Judge 1996). Responders after 12 weeks could be included in a maintenance study, and a proportion of the PXOS patients were later followed up independently of the drug company and further examined concerning comorbidity, personality dimensions, etc. (Bejerot et al. 1998 a, b).

*Inclusion criteria were:* aged between 18 and 75 years, suffering from OCD according to DSM-III-R criteria (American Psychiatric Association 1987) and at least six months duration of OCD. Also required were: a baseline score of 7 or more on the NIMH-GOCS (Insel et al. 1983) and a baseline score of 16 or more on the Y-BOCS (Goodman et al. 1989 b), i.e. at least moderately severe OCD cases.

*Exclusion criteria were:* a primary diagnosis of another psychiatric disorder, e.g. schizophrenia, bipolar disorder, major depressive disorder, currently or within the previous three months, risk of suicide, substance abuse (however, patients with anxiety or depressive symptoms, even panic disorder, considered secondary to the OCD could be included). Further exclusions were: any serious concomitant medical condition, a history of seizures, recent use of any psychotropic drugs (within 14 days of baseline, 28 days for depot neuroleptics and 3 months for antidepressants), or clinically significant electrocardiogram or laboratory findings. Pregnant or lactating women were also excluded. Patients that had ever been treated with PXT were excluded (according to the policy of the multicentre trial), but those previously treated with other SSRIs or CMI were included after at least 3 months' washout period of these drugs. This longer wash-out period for SRIs was imposed by us, specific for our centre, in order not to

[11] At that time, PXT was still being developed, and was later launched by Novo Nordisk A/S and Smith-Kline & Beecham Ltd. These companies were our collaborators in the study; see the preface of this thesis for more details on this.

interfere with the results of the biochemical measurements of serotonin (Ross & Åberg-Wistedt 1983).

Our centre included altogether 45 OCD patients. Out of these, 36 patients (17 men and 19 women) participated in our site-specific biochemical extension of the trial. Of these 15 were married or cohabiters. Mean age was 40.7 years (±12.7, range 18 – 74 years). Mean age of onset of OCD was 14.5 years (±6.5). Mean duration of OCD was 26.2 years (±14.8). Their mean Y-BOCS score was 25.3 (±5.9) at baseline, which is considered as rather severe OCD. On the MADRS, the mean score was 12.2 (±7.8), i.e. below the limit of mild depression. When included in the study, 24 patients (67 %) were SRI-naïve and none of them had been taking antidepressant agents during the preceding three months. The biochemical study included whole blood levels of serotonin and tryptophan, plasma levels of oxytocin and cholecystokinin (all as repeated measures at baseline, after 1 week and after 4 weeks of treatment) and serum concentration of the antidepressant drugs (paroxetine and clomipramine, including desmethyl-clomipramine, after 1 week and after 4 weeks). Information on sexual function ratings on at least one time point was available for 35 of the 45 patients. Both biochemical results and sexual function were available in 31 patients (15 men and 16 women). Of these 17 were singles and 14 were cohabiters. Mean age was 40.8 years (±11.1, range 18 - 57 years). Mean age of onset of OCD was 13.9 years (±6.7). Mean duration of OCD was 26.9 years (±13.0). Their baseline mean Y-BOCS score was 25.1 (±5.7) and their MADRS mean score was 11.9 (±7.8).

## 3.2 Diagnostics and rating scales used

### 3.2.1 Diagnostic methods

Every patient that was included in the studies of this thesis was interviewed face-to-face and diagnosed by an experienced psychiatrist. Out of the 402 patients included in the psychometric testing of BOCS (paper I), 42 patients had been diagnosed earlier, according to DSM-III-R (APA 1987), while the other patients were diagnosed according to DSM-IV (APA 1994). They were assessed through the Structured Clinical Interview for DSM-IV – Axis I Disorders (SCID-I; First 1996) or a structured DSM-IV-based clinical interview (as described in paper II).

The patients for the PXOS were diagnosed by means of a structured interview, covering the diagnostic criteria of DSM-III-R for OCD, anxiety disorders and affective disorders. Obsessive-compulsive disorder subtypes

and comorbidity were categorized as history of or presence of panic attacks, tics, overvalued ideas (= poor insight) and autistic personality traits (Bejerot et al. 2001).

### 3.2.2 General functioning/severity measures

All patients in the PXOS trial were evaluated on the Clinical Global Impression (CGI) measures, both the CGI Severity of illness and the CGI Improvement scales (CGI-S and CGI-I, respectively; Guy 1976). In addition, the patients rated their own improvement on the self-rating version of the CGI-I: the Patients' Global Evaluation (PGE). These three scales have one single item with seven scale steps.

In paper I, the Global Assessment of Functioning (GAF; APA 1987, 1994) was also implemented. This is a one-item scale ranging between 1 and 100, intended to cover functional impairment as well as illness severity.

### 3.2.3 OCD scales used

#### 3.2.3.1 Y-BOCS

The Y-BOCS (Goodman et al. 1989 b, c) was the main outcome measure and a primary efficacy variable of the PXOS trial. This scale is preceded by a symptom checklist with 58 items, describing various OCD symptoms (Leckman et al. 1997). Each of these symptoms can be endorsed as currently present, previously present or never present. Then the subject's main obsessions and compulsions should be listed. Finally, the severity is rated on 5 items concerning obsessions and 5 items concerning compulsions. Each item is rated 0 – 4, adding to a total score ranging between 0 and 40. Scores of 16 – 23 are considered moderate severity, 23 – 32 is severe and 33 or above is extremely severe OCD. Y-BOCS has been viewed as the gold standard of OCD rating, in spite of some shortcomings (e.g. Deacon & Abramowitz 2005). A revised version, the Y-BOCS 2nd edition (Y-BOCS-II), was developed, based on the criticism (Storch et al. 2010 a, b). In our studies, however, we used the original version.

#### 3.2.3.2 NIMH-GOCS

The NIMH-GOCS was first used in a pharmacological OCD trial (Insel et al. 1983) and is based on previous global scale (Murphy et al. 1982). The NIMH-GOCS is a single-item global rating of OCD illness severity that ranges from 1 (normal) to 15 (very severe). A rating of 7 or above corre-

sponds to a clinical degree of severity for cases of OCD. This scale has demonstrated excellent test – retest reliability, and the correlation with Y-BOCS severity rating is high (Kim et al. 1992). It was defined as a second primary efficacy variable in the PXOS trial.

### 3.2.4 Depression scale used

Throughout the PXOS trial, the MADRS (Montgomery & Åsberg 1979) was used for assessing comorbid depressive symptoms. This is one of the most commonly used rating scales for depression, with 10 items, each scored from 0 to 6, thus producing a total score ranging between 0 and 60. The threshold value for moderately severe depression has been defined as a score of 20 (Snaith et al. 1986).

### 3.2.5 Scale for evaluation of autistic traits

All the patients included in the PXOS trial and a proportion of those in the BOCS study were evaluated by means of the High functioning autism/Asperger Global Scale (HAGS; Bejerot et al. 2001). This is a one item global assessment, based on the clinician's thorough information about the patient, scored between 0 and 4.

### 3.2.6 Sexual functions scales

#### 3.2.6.1 The Limited symptom checklist and the Sexual symptom checklist (SSCL)

By means of a semi-structured interview, the "Limited symptom checklist", administered by the clinician, some specific, anticipated adverse effects were supposed to be quantified in the PXOS. This checklist was included in the trial in spite of not having been tested for reliability or validity. The multi-centre results of this scale were never published or presented, as far as we are aware. However, the detailed information on sexual functions made it useful for a closer enquiry into the sexual side effects of SRI treatment.

Eight of the 14 items on this checklist concern sexual functions, closely following the items reported in an early study of clomipramine-induced anorgasmia (Monteiro et al. 1987). These items are (verbatim) as follows: (a) Your interest in sex, (b) Sleepiness interfering with sexual function, (c) Frequency of sex/masturbation, (d) Erection (males)/lubrication (females), (e) Sexual sensation, (f) Intensity of orgasm, (g) Difficulty or increased time to reach orgasm, and (h) Intensity of pain at orgasm. Each item was

graded "none", "low", "medium" or "high". The clinician was instructed to perform this interview at baseline and at each visit during the 12 weeks' trial. For the present study, the sleepiness and the pain items (items b and h) were excluded, due to irrelevance and low endorsement rate, respectively. The six remaining items, here labelled the "Sexual symptom checklist" (SSCL), are strikingly similar to the Arizona Sexual Experience Scale (ASEX; McGahuey et al. 2000), commonly used in psychopharmacology studies. Each item of the SSCL was graded 0-1-2-3 and included in our analyses as Likert-type items. Since, for all items but "difficulty or increased time to reach orgasm", higher points denote improved/increased sexual function, we reversed this item. We could then sum up the six items to an SSCL total score, approximating general sexual functioning.

#### 3.2.6.2 Comparison of the SSCL with the ASEX scale

As mentioned above, the "Limited symptom checklist" was an unvalidated, "ad hoc" scale for the multicentre study, and the results were not included in the main publication of this trial (Zohar & Judge 1996). Therefore, in order to validate the SSCL, we mathematically transformed our SSCL scores in order to simulate the differently scored but otherwise similar ASEX scale (five items, scored 1-6; McGahuey et al. 2000). For this purpose, grade 0 (very poor function) on SSCL was replaced by 6, grade 3 (optimal function) by 1, and the other grades correspondingly in between (with the reversed item fitted accordingly). Among the five ASEX items, two ("penile erection/vaginal lubrication" and "ability to reach orgasm") are almost exactly equivalent to two items on the SSCL; and ASEX' "satisfaction from orgasm" corresponds well with SSCL's "intensity of orgasm". Of the remaining SSCL items, "interest in sex" and "frequency of sex" may reasonably substitute for "arousal" and "drive", respectively, on the ASEX scale, making the last SSCL item, "sexual sensation", superfluous. By means of this transformation, our scores could be directly compared to ASEX scores from two published studies (Fontenelle et al. 2007, Kendurkar & Kaur 2008), where OCD patients were compared to other psychiatric subjects and healthy controls concerning their sexual function.

In addition, we probed the validity of the SSCL for our aims by testing its ability to detect differences between the sexes and changes induced by SRI treatment, as has been reported by means of the ASEX scale (McGahuey et al. 2000).

### 3.2.7 Definitions of response used

The range of different response criteria within OCD research has already been discussed briefly in 1.6.8.1. In the PXOS trial, the response criteria were decided at the multi-centre level as *at least 25 % reduction of initial Y-BOCS score and at least 2 points improvement on the CGI-Severity of illness (CGI-S) scale.*[12] In most other trials including the CGI scales, the CGI-Improvement subscale is used to record improvement and response, why the use of CGI-S for this purpose was unusual.

In our WB-5HT study (paper II), we chose to sharpen the criteria to *at least 35 % reduction of initial Y-BOCS score, and a score of 1 or 2 on the PGE (Patients' Global Evaluation)*. PGE is the patients' self-rated version of the CGI-I scale. Our intention with choosing the PGE was that inclusion of the patients' perspective, as a complement to the clinician rating, would ensure a better validity of the response categorisation.

Later, when calculating data on the same group of patients for paper IV-V, it appeared that most studies using 35 % decrease on Y-BOCS did not qualify this further by also requiring CGI or PGE limits, while those using 25 % on Y-BOCS regularly did so (see e.g. Fineberg et al. 2012). Accordingly, in order to comply with the scientific community and make our results easier to compare with other studies, in paper IV-V we then again changed our response criteria to *at least 25 % reduction of initial Y-BOCS score, and a score of 1 or 2 on the PGE.*

Interestingly, the recent international consensus on response criteria for OCD (Mataix-Cols et al. 2016) are very similar to those we chose to use in our work from 2001 (paper II).

## 3.3 Methods for development and evaluation of the BOCS scale

### 3.3.1 Incentives for a new scale

The work with the BOCS scale started with our experiences of using the Y-BOCS in the PXOS trial. It became clear that a shorter scale that was easier for the everyday patient to grasp would be both clinically useful. Ideally, this scale should be useful both as a self-rating scale and as a clinician-rated scale. In spite of decreased comprehensiveness, the new scale

[12] It should be noted that two points decrease on CGI-S is not the same as a score of 1 or 2 on CGI-I. The first is a relative improvement anywhere on the severity dimension; the latter is the clinician's assertion of a major improvement.

should be able to support the diagnosis of OCD among clinical psychiatric patients and to rate their severity.

Susanne Bejerot started the project and carried out almost all the work with the development of the BOCS scale.

### 3.3.2 Rearranging, rewording and pruning of the symptom checklist

To begin with, we retained the basic structure of the Y-BOCS, with a symptom checklist and a separate severity rating. In order to reduce the length of the checklist, we wanted to ensure that we kept the most relevant items. For this purpose, we used a comprehensive list of items, derived from the self-report versions of the Y-BOCS and the CY-BOCS. This resulted in a 62-item checklist, divided into thematic sections, roughly in accordance with the 13 main pre-set symptom categories of the Y-BOCS (Goodman et al. 1989 b, c, Bloch et al. 2008). We then rearranged the order of the checklist items so that an item related to a specific compulsion immediately followed an item related to the corresponding obsession. For example, "I am concerned that I may contaminate others by spreading dirt or germs" was followed by "I wash my hands excessively or in a ritualized way in order to avoid contamination", with examples provided.

We then rephrased the examples of obsessions/compulsions, provided with each checklist item, into less personal, more casual formulations, in order to make them less threatening to the patient and to provide a more suitable support for self-rating. We tried to achieve this by, for example, replacing "you" with "one". Furthermore, the type of obsession, e.g. whether it was the need for "the just right feeling" or a magical (i.e. superstitious) belief that preceded the ritual, was specifically targeted in order to distinguish different justifications for the compulsion. The Y-BOCS does not accommodate for this distinction, but it has been considered of great clinical relevance concerning the thematic categorisation of the symptoms. For each checklist item, the patient was requested to specify whether the symptom was present "right now" (i.e. during the past week), "in the past" or "has never been present". This scoring was retained from the Y-BOCS symptom checklist.

Next, we set out to uncover the hierarchical structure of this comprehensive 62-item checklist with 13 thematic sections. For this purpose, 61 OCD patients completed this version. The final symptom checklist items were selected to fulfil the following criteria: 1) if any of these 61 patients had endorsed only one item within any of the thematic sections, this item should be selected, 2) for those patients that endorsed more than one item

within a section, at least one of these items should be selected. As within each thematic section, some items were much more often endorsed than others were, it turned out that only one or two items per section were necessary in order to fulfil these requirements. Thus, we considered the remaining items superfluous and excluded them from the checklist.

### 3.3.3 Finalising the BOCS for clinical use

This "pruning" of the Y-BOCS/CY-BOCS symptom checklist resulted in 12 hierarchically superordinate and supposedly, from a clinical perspective, highly relevant items for the identification and assessment of OCD. Two further items included in the Symptom Checklist were related to hoarding and body dysmorphic disorder and thus relevant for the DSM-5 category "Obsessive–compulsive related disorders". In addition, one item reflecting self-harm (included in the Miscellaneous compulsions section of the Y-BOCS checklist) was added, based on the clinical observation that patients with comorbid ASD, tic disorders and/or emotionally unstable personality occasionally harm themselves in a compulsive or ritualized manner. Because of its clinical weight, we considered this item important to include.

After this process, the BOCS consisted of a 15-item Symptom Checklist accompanied by a compound six-item Severity Scale for obsessions and compulsions combined. It encompasses the revisions made in the Y-BOCS-II severity scale (Storch et al. 2010 a, b) by including obsessive-compulsive free intervals, extent of avoidance and by excluding the resistance item. Finally, to compensate for the merged severity assessment of obsessions and compulsions, a global measure of the proportion of obsessions *versus* compulsions was included between the symptom checklist and the severity rating.

For the psychometric testing of the BOCS scale, 402 psychiatric patients were included, see 3.1.1.

## 3.4 Biochemical methods

### 3.4.1 Analysis of serotonin and tryptophan in whole blood (Papers II-III)

In the 1980s, in her research laboratory at Lillhagen hospital in Gothenburg, Margareta Larsson developed a robust method, suitable for clinical routine, measuring both serotonin and tryptophan (the amino acid precursor of serotonin) from one sample of whole blood (Larsson et al. 1988). In two preliminary studies, we found that one to two months' treatment with

clomipramine (Humble et al. 1988) or citalopram (Humble & Wistedt 1992) reduced the whole blood serotonin (WB-5HT) levels almost uniformly to very low levels with no meaningful differentiation between individuals, essentially providing a measure of cumulative treatment compliance. On the other hand, this method proved sensitive enough to detect a subtler decrease of WB-5HT in patients treated with the antihistamine dex-chlorpheniramine (Hellbom et al. 1999), previously shown to be a serotonin uptake inhibitor (Carlsson & Lindqvist 1969 c). In the present investigation (PXOS), we therefore chose to measure WB-5HT at baseline, after one and after four weeks' treatment with SRI or placebo, in the hope of finding a more informative differentiation between individuals. Regrettably, at the time of the PXOS study, the laboratory at Lillhagen had been shut down, why we instead collaborated with Peter B.F. Bergqvist and Finn Bengtsson, then at Lund University. They implemented the method of Margareta Larsson, and the samples were analysed at their laboratory.

Blood samples were collected at baseline (i.e., before any drug treatment had started), after 1 week of treatment, and after 4 weeks of treatment. Between 8:00 AM and 9:00 AM, 5 mL of blood was drawn by antecubital venepuncture, using heparinized Vacutainer tubes. Aliquots of 2 mL of blood were then transferred into glass vials containing 0.1 mL ascorbic acid (6%; Merck, Darmstadt, Germany). All samples were frozen in -20°C and kept at this temperature until time of analysis.

The 5-HT content of the whole blood samples was determined by means of a high-performance liquid chromatography (HPLC) assay as previously described (Larsson et al. 1988) with minor modifications. In brief, 200 µL of blood was mixed with 100 µL of the internal standard (IS) N-methyl-serotonin oxalate (Sigma, St. Louis, MO), 50 µL EDTA (10%; Merck), and 50 µL ascorbic acid (25%; Merck). After mixing the tubes gently an aliquot of 50 µL of HClO4 (3.4 M; Merck) was added. Each test tube was then mixed for 10 secs and stored in 4°C for 10 min. The test tubes were then mixed again and centrifuged for 10 min at 14,000 rpm. An aliquot of 20 µL of supernatant was injected onto the HPLC system by the use of an auto-sampler (Waters M-717; Waters, Sundbyberg, Sweden). The mobile phase consisted of 0.01 mol/L citrate buffer (pH 4.1) and HPLC-grade methanol in a proportion of 95:5 (vol/vol). The mobile phase was delivered at 0.4 mL/min through a twin-reciprocating pump (LKB-2150; LKB-Produkter AB, Bromma, Sweden). The samples were separated at 30°C on a 2.0-mm X 15-cm stainless steel column (Ultrasphere, ODS C18, 5 µm; Beckman Instruments, Fullerton,

CA). Serotonin and IS were detected by a fluorescence detector (Ex = 280 nm, slit 10 nm; Em = 345 nm, slit 10 nm; Perkin Elmer [Boston] 650-10LC), and the detection signals were recorded and processed for quantification on a Waters computer system (Waters Maxima). The detection limits for 5-HT were in all cases found to be about 10–25 nmol/L (signal/noise ratio = 3).

### 3.4.2 Oxytocin in plasma

Blood samples were obtained by cubital venepuncture, between 8h00 and 9h00 a.m., when patients had been fasting from midnight and before the morning dose of medication was taken. The sampling was performed by one of two nurses, known to the patients, on each occasion in the same quiet room, at normal room temperature and under comfortable circumstances. Samples were taken at baseline, after 1 week's double-blind treatment and after 4 weeks of treatment. The samples were collected in tubes containing heparin (10 IU/mL) and Trasylol (500 IU/mL) and centrifuged. Plasma was separated, frozen at -70° C, and blindly analysed in the same assay. The concentration of oxytocin was measured with a specific radioimmunoassay described by Stock and Uvnäs-Moberg (1988). Briefly, plasma samples were extracted on SEP-PAK $C_{18}$ cartridges prior to assay. The recovery of this extraction procedure was 95.3 ± 10.1 %. For the assay, antiserum K19 (Milab, Malmö, Sweden) was used, which has a cross-reactivity at 70% relative binding (B/BQ) of 0.01% with arginine(A)-vasopressin, <0.01% with lysine(L)-vasopressin and 0.1 % with A-vasotocin. The limit of detection is 2 fmol/mL and the intra- and inter-assay coefficients of variation are 11.2 and 13.0% respectively.

### 3.4.3 Antidepressant drugs in serum

When analysing the antidepressant drug concentrations, the serum samples were considered as reasonable steady-state trough values. Paroxetine and clomipramine serum concentrations were analysed after extraction by means of high performance liquid chromatography with UV-detection as described elsewhere (Reis et al. 2004). With this method, expected serum concentrations from patients treated with 40 mg paroxetine/day are (median (interquartile range)) 125 (105-400) nmol/L.

In order to enable statistical calculations of the two drugs together, we generated z scores of the drug levels for use in combined analyses.

## 3.5 Statistical methods

For paper I, the statistical calculations and analyses were performed with SPSS version 19. Data were summarized using standard descriptive methods, such as frequency, means, and standard deviation. The intercorrelation matrix was studied through principal component analysis (Oblimin rotation). Five factors were extracted (adjusted for low (<0.35) communalities). For calculations of sensitivity and specificity, cross-tables and the Receiver Operating Characteristics (ROC) curves between diagnosis and score were established. Scores were then dichotomized using values as close to the median as possible. Internal consistencies were expressed as Cronbach's alphas and mean inter-item correlation coefficients. Correlations between total BOCS scale scores, and age, GAF, and NIMH-GOCS were expressed as non-parametric Kendall's rank correlation coefficients ($\tau$). The correlation between the obsessions and compulsions in Y-BOCS and BOCS was expressed as Pearson's product-moment correlation coefficient. Differences between diagnostic groups in age and GAF scores were analysed with one-way analysis of variance (ANOVA) and *post hoc* tests with Tukey's honestly significant difference (HSD) test. Differences between diagnostic groups in item scores were analysed with non-parametric Kruskal-Wallis' test also corrected for multiple testing. The significance level in all analyses was set at 5 % (two-tailed).

In papers II and III, we used only basic statistics, like two-tailed Student's t-tests and Pearson's correlation coefficient.

In papers IV and V, based on previous literature on oxytocin, no prediction of the expected direction of findings was possible. The patients treated with paroxetine and clomipramine were merged to an SRI group, as no meaningful differences between these two groups were found. Since most oxytocin measurements were non-normally distributed, all values are reported as medians with interquartile range (IQR = 1$^{st}$ and 3$^{rd}$ quartiles) in parentheses, and nonparametric tests (Mann–Whitney U-test [MW] and Spearman Rank Order Correlation) were utilised. ANOVA of repeated measures turned out invalid due to the non-normal distributions. This and low sample size prevented multivariate methods to be used. Thus, we were confined to implement nonparametric tests of the measures and of the differences between the repeated measures.

In paper IV, we also calculated the intra-individual range of oxytocin variability. We had obtained three repeated measurements in most of the patients (n=32) and two measurements in the remaining four. This enabled calculation of the difference between the maximal and minimal plasma

oxytocin levels for each individual, the "oxytocin range". We intended this to be interpreted as a measure of the flexibility or responsivity of the individual's oxytocinergic system.

In all papers, probabilities $< 0.05$ were assumed as significant and, when relevant, Bonferroni's adjustment for multiple comparisons was judiciously implemented in paper IV. However, due to the explorative nature of this study, also the non-adjusted results are presented.

In papers II and III, all statistical computations were made with StatView 4.12, Abacus Concepts (Berkeley, CA), for Macintosh. In papers IV and V, we used Statistica 64, version 10, StatSoft Inc.

# 4 Ethical considerations

The Research Ethical Committee of the Karolinska Hospital, Solna (Chairperson Rolf Nordlander), approved the PXOS study on treatment of OCD, on the 7th of October 1991 (d-Nº 91:214). This trial formed the basis of papers II – V. In accordance with the recommendations of the committee, the patients received detailed written information about the study, and witnessed oral informed consent was obtained from every patient before enrolment. Hence, a third person (nursing staff) was present to testify to each informed consent, to ensure that no undue enforcing was involved. A signature by this third person evidenced this testimony in the record files. This was a deviance from the ethical practice recommended in other countries participating in the multi-centre trial, where the patients themselves were expected to provide a written consent. However, at the time of the study, Swedish ethical committees routinely disapproved of trials demanding informed consent, written by the patient. This was based on the assumption that such practice made the patient feel inappropriately committed to fulfil the trial.

Another ethical issue concerning the PXOS was whether we could use advertising in order to include patients with OCD or not. At the time, the ethical committees usually rejected this practice, based on experience from depression studies, where less severe cases, not necessarily in need of treatment, might be included. However, concerning the rarity of OCD patients in clinical practice and the number of cases that likely go untreated, we argued that advertising would considerably increase the likelihood of including relevant patients for our study. The committee accepted our arguments, and the majority of the patients that were recruited by advertisement turned out to have a long duration of untreated, often quite severe OCD.

The Swedish Medical Products Agency (Läkemedelsverket), unit of pharmacotherapy, also approved the PXOS randomized, placebo-controlled trial, on 14th of January 1992 (d-Nº 151:1544/91).

Since the PXOS trial was a commissioned trial in collaboration with the pharmaceutical company, the access to data from the trial may give rise to ethical conflicts. This is regulated in the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/index.html). According to this, "it must be possible to make all study results publicly accessible. The praxis, in accordance with the rules of research ethics, is that collaborating researchers in research carried out as an assignment shall

also have access to unprocessed results, with applicable reservations as dictated by business confidentiality" (quoted from the Swedish Ethical Review Boards, www.epn.se). In our case, the business confidentiality resulted in an agreement that the company had to approve any publications based on the data. Due to the time that has elapsed since the trial took place, we have not asked for approval concerning papers IV and V.

The original project of initial development of the rating scale BOCS was approved by Ulf Ulmsten, chairperson of the Research Ethics Committee of the Faculty of Medicine, Uppsala University, on 17th of April 1996 (d-№ 96:109).

The Regional Ethical Review Board in Stockholm (Chairperson Claes-Robert Julander) approved the project to test whether the BOCS rating scale had acceptable psychometric properties (paper I), on the 15th of December 2009 (d-№ 2009/1579-31/5).

# 5 Results

## 5.1 Support for the clinical usefulness of BOCS (paper I)

### 5.1.1 Gender ratio and global functioning among participants

The gender ratio varied across the diagnostic groups, with a male predominance among the patients with ASD and more females in the OCD group ($\chi^2 = 11.96$, $df = 3$, $p = 0.008$). Mean Global Assessment of Functioning (GAF) scores (APA 1987 & 1994) were significantly lower in patients with ASD compared to the other groups ($p \leq 0.05$ in a *post hoc* analysis).

### 5.1.2 The Symptom Checklist

Eight of the Symptom checklist items, namely checking, contamination, washing, ordering, repeating, need for just right feeling, fear of harming and superstition (listed from highest to lowest endorsement) distinguished the OCD patients from all the other diagnostic groups. The sexual obsessions item endorsed by 18 % of the OCD group, distinguished the OCD group from the ASD and the mixed psychiatric groups but not from the ADHD group. Likewise, the morality issues item, endorsed by 32 % of the OCD patients, distinguished them from the mixed group but not from the other groups. Finally, five items, i.e. fear of losing control, religious obsessions, hoarding, somatic obsessions and self-harm, did not differ between any of the four diagnostic groups. When the Symptom Checklist was used as one homogenous dimension, i.e. the number of endorsed items were summed up and used to predict the diagnosis of OCD, the sensitivity of the checklist sum was 85 %, the specificity varied between 62 and 70 % and the internal consistency (Cronbach's $\alpha$) was 0.81. Taken together, all these measures indicate useful clinical properties of the Symptom Checklist.

### 5.1.3 The factor analysis of the Symptom Checklist

We then entered all the items from the Symptom Checklist in a principal component analysis. Five subscales emerged, and we labelled them "Symmetry", "Forbidden thoughts", "Contamination", "Magical thoughts" and "Dysmorphic thoughts". The OCD group scored higher than the other psychiatric diagnostic groups on all subscales with the largest difference for "Contamination" ($F_{3, 398} = 26.25$, $p < 0.001$). Furthermore, *post hoc* Tukey's honestly significant difference (HSD) tests revealed significant

differences between the OCD subjects and the other diagnostic groups on most subscales. The exception was the "Magical thoughts" subscale, where the OCD group did not differ significantly from the mixed psychiatric group. The mean inter-item correlation for the total Symptom Checklist was 0.22.

### 5.1.4 The Severity Scale

The OCD patients scored significantly higher on each item in the severity scale compared to the other diagnostic groups. The factor analysis performed on the items from the Severity Scale yielded a single factor, supporting homogeneity. The mean cut-off score was 1.50, and divided the sample into two groups of severity (low = 65 % *vs* high = 35 %). Seventy-two percent of the OCD patients were correctly identified, as were 75 % of the ASD patients, 76 % of the ADHD patients, and 84 % of the patients with mixed psychiatric disorders. The severity Scale showed a sensitivity of 72 %, a specificity ranging between 75 and 84 % and a Cronbach's α of 0.94 (one factor).

## 5.2 WB-5HT changes and anti-obsessive response (paper II-III)

### 5.2.1 Primary outcome results

The primary outcome of this study was the changes of WB-5HT during SRI (clomipramine or paroxetine) treatment of OCD in relation to treatment response. We measured WB-5HT at baseline, after 1 week and after 4 weeks of treatment.

First, we compared the evolution of WB-5HT between the SRI treated and the placebo treated patients, in order to identify the expected effect of SRI *per se* (that is, irrespective of anti-obsessive response), thus validating our method. At baseline, before treatment, the WB-5HT ranged between 0.27 and 1.40 µM (mean 0.65, n = 36, SD ± 0.25). The 9 placebo patients did not change significantly: 0.63 ±0.32 after 1 week and 0.65 ± 0.28 after 4 weeks of treatment. The 27 SRI treated patients, however, decreased markedly: 0.23 ± 0.11 after 1 week and 0.02 ± 0.01 after 4 weeks of treatment. Compared to baseline, the WB-5HT of the SRI-treated group had decreased by 92-99 % after 4 weeks, i.e. to levels close to or under our detection border (0.01 µM). Twelve cases (all on PXT) had reached 0.01 µM after four weeks. Accordingly, the distribution of WB-5HT levels in the SRI-treated group was considerably wider after one week (SD ± 0.11) than after four weeks (SD ± 0.01), when the decrease was uniformly max-

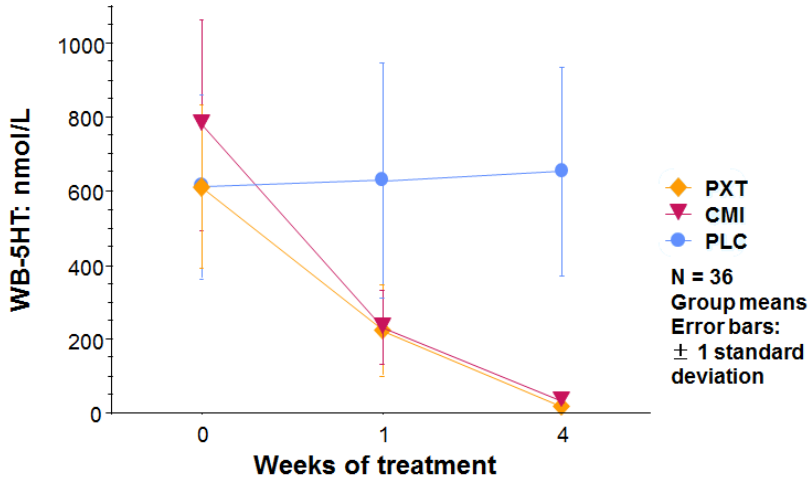


*Figure 1. Evolution over 4 weeks of serotonin in whole blood (WB-5HT) during treatment with the serotonin reuptake inhibitors paroxetine (PXT) or clomipramine (CMI), compared to placebo (PLC). 1000 nmol/L = 1 μM.*

imal. The very low levels after 4 weeks of treatment appeared to reflect medication compliance among the patients, but did not differentiate between responders and non-responders; see *Figure 1* for summary.

Then, we related the changes of WB-5HT to anti-obsessive response, as reflected by changes of Y-BOCS scores. There was a highly significant negative correlation between the decrease of WB-5HT after *one* week of SRI treatment and the decrease of Y-BOCS after 12 weeks of treatment (or at last observation) ($r$ = -0.61, $n$ = 27, $p$ = 0.0006). Also for the PXT treated patients, this correlation was highly significant ($r$ = -0.71, $n$ = 18, $p$ = 0.0009). That is, the patients whose WB-5HT decreased the most in the early phase of SRI treatment had the worst anti-obsessive result at endpoint. As expected, we found no such correlation in the placebo group. A scattergram of the correlation is presented in *Figure 2*. Responders to SRI (according to our stricter criteria, see 3.2.6) had a WB-5HT decrease of 56 % and non-responders decreased by 74 % ($t_{25}$ = 3.26, $p$ = 0.0032).

In contrast to these findings based on the one weak sample, the WB-5HT decrease after four weeks of SRI treatment did not correlate with anti-obsessive outcome after 12 weeks ($r$ = -0.015, $n$ = 24, $p$ = 0.94).

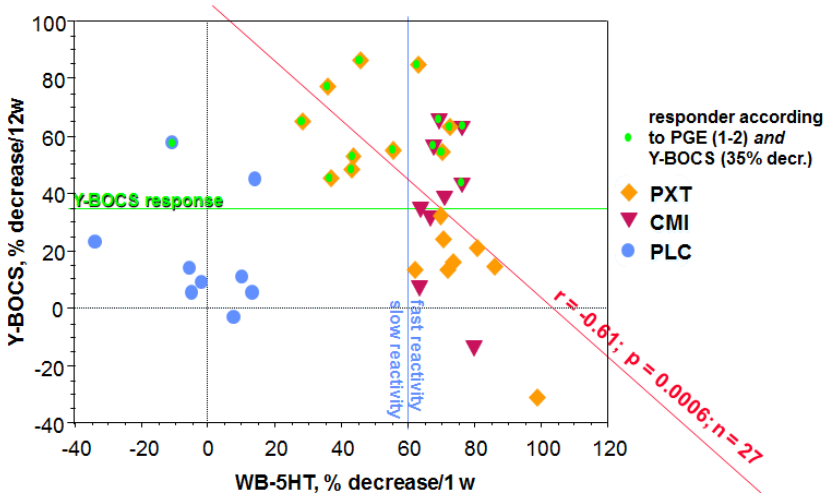


*Figure 2. Relation between change of serotonin in whole blood (WB-5HT) after 1 week of treatment and anti-obsessive response after 12 weeks of treatment. The "Y-BOCS response" line indicates 35 % decrease on the Y-BOCS, i.e. the higher above this line, the better the response. CMI = clomipramine, PGE = Patients' Global Evaluation, PLC = placebo, PXT = paroxetine, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.*

### 5.2.2 Other findings

The baseline levels of WB-5HT in our untreated OCD patients ranged between 0.27 and 1.40 µM (mean 0.65, SD 0.25). Furthermore, there was a negative correlation between WB-5HT and the initial severity of OCD (as measured on the Y-BOCS scale) at baseline ($r = -0.35$, $n = 36$, $p = 0.038$). WB-5HT also differed between samples taken in the summer half-year (0.60 µM, SD 0.15) and those taken in winter (0.83 µM, SD 0.36; $t_{25} = 2.34$, $p = 0.028$).

## 5.3 Oxytocin levels in SRI treated OCD (paper IV)

### 5.3.1 Oxytocin changes related to treatment response

Highly significant correlations between dynamic changes of plasma oxytocin during the first four weeks of SRI treatment and clinical improvement of OCD were found in this study. Significantly higher plasma oxytocin

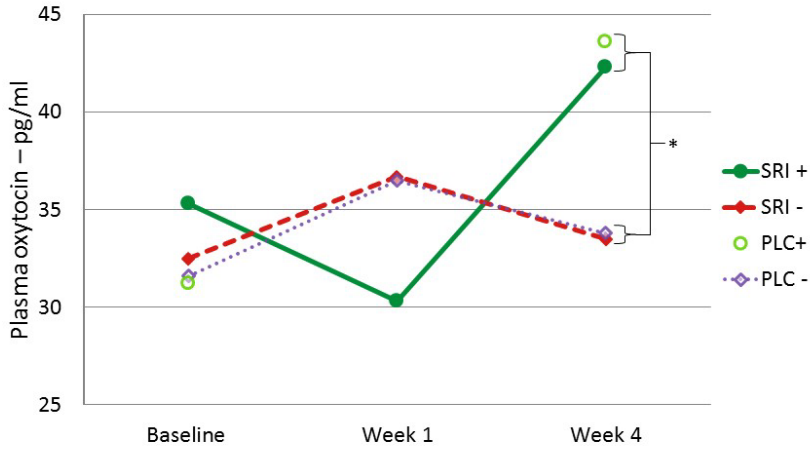


*Figure 3. Mean plasma oxytocin levels (pg/mL) during the first four treatment weeks among SRI responders (SRI +, n = 16), SRI non-responders (SRI -, n = 11), placebo responder (PLC +, n = 1) and placebo non-responders (PLC -, n = 8), respectively. Significant differences on Mann Whitney U-test were found: at week 4 between all responders and all non-responders; at week 4 between SRI responders and SRI non-responders; the change from week 1 to week 4 between SRI responders and non-responders (all p < 0.05).*
*Missing data: oxytocin at week 1 was missing for the only placebo responder; oxytocin at week 4 was missing in 3 other patients.*
*SRI = serotonin reuptake inhibitor; PLC = placebo, * = p < 0.05*

levels after 4 weeks of treatment were found among responders to SRI compared both to SRI non-responders and to placebo treated patients.

The effect of SRI treatment *per se* on oxytocin levels was determined by comparing SRI treated and placebo treated patients. Median plasma oxytocin (pg/mL) at the three time points for the SRI group and the placebo group, respectively, were: baseline 32.1 (IQR 22.7-39.5) vs 31.2 (22.6-39.5), after 1 week 30.4 (22.5-40.5) vs 36.1 (25.1-47.3), after 4 weeks 36.7 (27.3-43.8) vs 37.0 (26.1-43.6), and intra-individual range (over the three measurements) was 11.6 (5.1-16.8) vs 7.4 (5.8-12.4). None of these measures differed significantly between treatment groups.

However, when we compared changes of plasma oxytocin in responders and non-responders (as shown in *Figure 3*), oxytocin of responders first decreased and later increased, while the opposite was the case among non-

responders. For non-responders, this oxytocin trajectory was almost identical for SRI-treated and placebo-treated cases. Moreover, when we calculated the intra-individual range between the highest and lowest oxytocin value of the three measurements (supposedly reflecting the plasticity of the individual's oxytocinergic system), this differed markedly between responders (24.2 (IQR 15.7-37.5)) and non-responders (8.9 (4.9-12.7), MW $Z = 3.61$, $p = 0.0003$). Finally, the OCD patients with autistic traits ($n = 11$), had more restricted intra-individual oxytocin ranges (5.1 (3.5-9.7)) than the rest of the sample (15.6 (7.6-27.3), MW $Z = 2.76$, $p = 0.006$, missing data = 2).

### 5.3.2 Clinical correlates of baseline oxytocin levels

The oxytocin levels at baseline were not normally distributed; rather they seemed to belong to two or three modes. Oxytocin was unrelated to depressed mood (as measured on the MADRS), duration of OCD, age and sexual function prior to treatment, but showed a relationship to OCD severity as measured on the Y-BOCS (*rho* = 0.35, $n = 36$, $p = 0.037$), see *Figure 4*. This correlation apparently depended on the future SRI responders, among whom it was most pronounced (*rho* = 0.58, $n = 16$, $p = 0.019$); accordingly, among the SRI non-responders it was absent (*rho* = 0.24, $n = 11$, $p = 0.47$), as it was also among the collapsed non-responders (*rho* = 0.17, $n = 19$, $p = 0.48$). When considering the entire sample, the correlation at baseline between oxytocin levels and OCD severity was not confined to any of the OCD subtypes identified by us, as is evident from *Figure 4*.

A few other clinical variables were associated with baseline oxytocin levels: those with OCD onset before age 11 years (n = 12) had higher oxytocin (35.4 (31.7-47.3)) than those with adult onset (n = 11, median 21.3 (19.0-35.6), MW $Z = 2.12$, $p = 0.034$). The patients that completed the entire 12 weeks' trial had higher baseline oxytocin, 34.7 (25.8-40.0), compared to trial discontinuers (24.2 (20.5-30.2), MW $Z = 2.06$, $p = 0.039$). Finally, the distinct group of 6 patients in the mode with the highest baseline oxytocin levels (50 – 67 pg/mL) was significantly more likely to be cohabiting than those with lower levels of oxytocin ($\chi^2 = 4.41$, $df = 1$, $p = 0.036$).

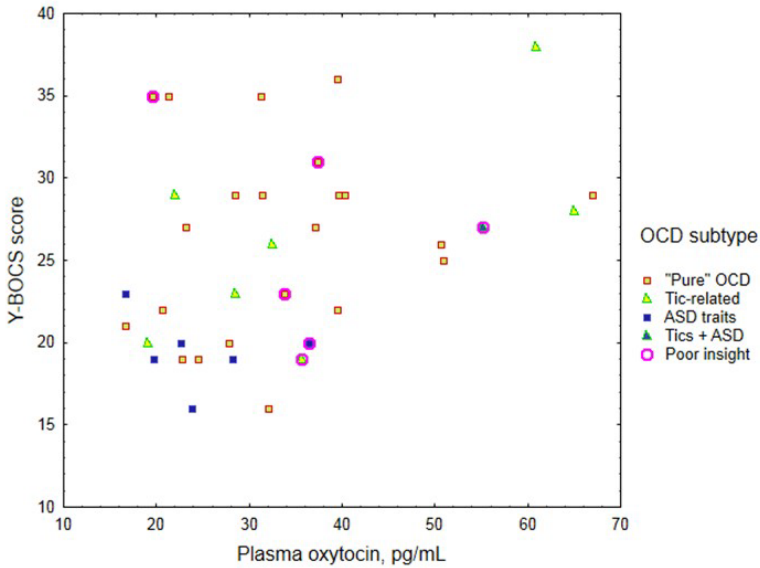


*Figure 4. Correlation between baseline severity of OCD and baseline plasma oxytocin (pg/mL), according to OCD subtypes. Severity of OCD was specified as total score on the Y-BOCS. Due to non-normal distribution of oxytocin, non-parametric analyses were performed: Spearman's correlation for the entire sample: rho = 0.35, n = 36, p = 0.037. ASD = autism spectrum disorder*

## 5.4 Oxytocin and SRI-induced orgasm dysfunction (paper V)

In this study we related changes of sexual functioning (as measured on the Sexual symptom checklist (SSCL), see 3.1.5.2) to changes of plasma oxytocin and serum levels of the SRIs. There was a relationship between higher oxytocin levels after 4 weeks SRI treatment and treatment induced delayed orgasm in OCD patients. Moreover, delayed orgasm in men was also related to anti-obsessive treatment response with SRIs. Mean serum concentrations of paroxetine was 116 nM and of clomipramine 230 nM. Only in one patient, the prescribed drug was not measurable, suggesting non-compliance. However, the markedly decreased WB-5HT level of this patient suggests that this just represented an occasional "drug holiday". The serum concentrations of the SRIs did not differ in relation to adverse sexual effects, decreased interest or delayed orgasm.

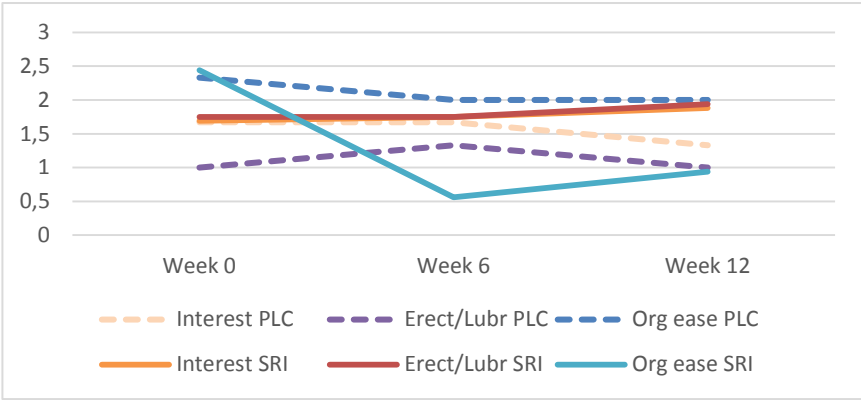


***Figure 5***. *Mean sexual functioning on selected items from the SSCL during 12 weeks among paroxetine/clomipramine or placebo treated patients with obsessive-compulsive disorder. Only patients with complete SSCL results from week 0, 6 and 12 are included. Erect = erectile function, Lubr = genital lubrication, Org ease = ability to reach orgasm, PLC = placebo, SRI = serotonin reuptake inhibitor, SSCL = Sexual symptom checklist.*

Thirty-two percent of the patients reported markedly decreased sexual interest and 73 % reported markedly impaired orgasm after 6 weeks of SRI treatment. In the placebo-treated group none reported decreased sexual interest and only 1 (20 %) reported impaired orgasm. The difference over time of sexual functioning between SRI and placebo treated patients is shown in *Figure 5*.

Treatment response was related to higher oxytocin levels, when the levels at 4 weeks of SRI treatment were split by the median ($p$ = 0.038). Seventy five percent of the patients that reported impaired orgasm at week 6 responded to SRI treatment, compared to 50 % of the patients without this side effect. For the men included in the study, but not for the women, the relationship reached significance ($p$ = 0.028).

# 6 Discussion

## 6.1 Our results in the context of other research

### 6.1.1 BOCS and other more recent OCD scales (paper I)

Today an array of self-reports for OCD are available but each of them has its limitations (for reviews, see Grabill et al. 2008, Matsunaga et al. 2010, and Overduin & Furnham 2012). In short, the self-rated version of Y-BOCS (Baer 1991, Rosenfeld 1992) is extensive, hampering its clinical use; the 18 items Obsessive-Compulsive Inventory – Revised (OCI-R; Foa et al. 2002) does not measure severity, and its discriminant validity has been questioned. The 41 items Padua Inventory-Revised (PI-R; van Oppen et al. 1995) has low convergence with Y-BOCS and limited concurrent validity (Burns et al. 1996, Anholt et al. 2009); the 24 items Padua Inventory-Paltine Revision (PI-PR; Gönner et al. 2010 a) requires further development and has insufficient discriminative power regarding harming impulses and other obsessions. The 30 items Vancouver Obsessional Compulsive Inventory-Revised (VOCI-R; Gönner et al. 2010 b) requires each item to be scored separately, deeming it time-consuming; the 25 items Clark-Beck Obsessive-Compulsive Inventory (CBOCI; Clark et al. 2005) lacks discriminative power against other psychiatric disorders. The 25 items Florida Obsessive-Compulsive Inventory (FOCI; Storch et al. 2007) has limited discriminant validity and low correlation with the Y-BOCS (Aldea et al. 2009). The 47 item Schedule of Compulsions, Obsessions, and Pathological Impulses (SCOPI; Watson et al. 2005) includes some impulse-control disorders that are not associated with OCD and, finally, the 20 items Dimensional obsessive-compulsive scale (DOCS; Abramowitz et al. 2010) presents repetitive questions that may affect its acceptability.

Interestingly, the authors of the more recently developed scale Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS; Rosario-Campos et al. 2006), have adopted the same principle as was done in the BOCS of rating obsessions and compulsions together, likely due to the difficulties of separating them from each other. However, instead their scale calls for repeated severity ratings for each of the six symptom "dimensions", making their scale considerably more time consuming.

When BOCS is compared with the alternative rating scales, to our knowledge, no other scale has been tested in such large groups of adults

with ASD, ADHD, social anxiety disorder and other psychiatric states. Moreover, the widespread use of BOCS within Swedish psychiatry (child and adolescent as well as adult) supports its acceptability from a clinical perspective. The condensed scope and the versatility of use, as self-rating or clinician rating, probably contribute to this.

### 6.1.2 Peripheral measurement of serotonin in OCD (papers II-III)

The primary results of this study turned out to be opposite to our expectations: there was a highly significant negative correlation between the decrease of WB-5HT after *one* week of SRI treatment and the decrease of Y-BOCS after 12 weeks of treatment. That is, the patients whose WB-5HT decreased the most in the early phase of SRI treatment had the worst anti-obsessive result at end-point.

The basis of this study was a somewhat simplistic idea of the nature of serotonergic mechanisms. In one article citing our work (Walther et al. 2003), our study is actually used as an example, when deriding all the previous research that have tried to find information on brain serotonin activity from peripheral blood or platelet studies. On the other hand, as discussed in the correspondence following our publication (Mulder et al. 2002, Humble et al. 2002 [paper III]), the results may be interpreted as related to inflammatory, immunological, even autoimmune mechanisms. At normal turnover rate, $10^{11}$ platelets per day are produced, and the life span of a platelet is 8-10 days (Kuter 1996, Kaushansky 2008). The turnover may increase e.g. due to inflammation or diabetes, which then causes a shorter platelet life span. In such a situation, the platelets that were present before SRI treatment and replete with serotonin will disappear at a higher rate. Accordingly, our WB-5HT measure during SRI treatment most likely largely depends on the ratio between the pre-existing replete platelets and the newly added platelets that are prevented by the SRI treatment to store serotonin. An elevated platelet turnover, e.g. due to inflammation, would cause a more rapid decrease of WB-5HT during SRI treatment. The individual in our study that had the most rapid decrease of serotonin also suffered from diabetes type 1 and vitiligo (both autoimmune disorders) and was later diagnosed with Asperger syndrome, supporting this interpretation of our results. Presently, much research within psychiatry is focussing on inflammatory and autoimmune mechanisms within the CNS and the gut-brain axis (Kato et al. 2013, Bergink et al. 2014, Kiecolt-Glaser et al. 2015, Shajib & Khan 2015). This is the case also concerning OCD (Swedo et al. 2012, Rao et al. 2015, Shalbafan et al.

2015), as discussed in 1.5.4. It is plausible then, that our quantification of different patterns of WB-5HT changes actually was able to identify individuals with an inflammatory subtype of OCD, and who, therefore, were less responsive to SRI treatment.

Another interesting finding is the seasonal differences of the WB-5HT levels. Our findings of higher levels in winter are in line with several other investigators (Badcock et al. 1987, Mann et al. 1992), and may be explained by recent research on the effects of vitamin D on serotonergic functions (Patrick & Ames 2014). According to these authors, the enzyme tryptophan hydroxylase 1 (TPH1, necessary for serotonin synthesis in the gastrointestinal system and thereby influencing the levels in peripheral blood) is *negatively* regulated by calcitriol (the genomically active form of vitamin D). Accordingly, if vitamin D and calcitriol availability is lower in winter (which is normally the case), then the activity of TPH1 will increase, contributing to wintry elevation of serotonin levels in the peripheral blood, actually what we found in our OCD patients. Interestingly, TPH1 is also responsible for serotonin synthesis in the pineal gland, which requires serotonin in order to form melatonin, also often elevated in wintertime. Importantly, however, in the rest of the brain, serotonin is synthesised by means of the enzyme TPH2, which is *positively* regulated by calcitriol, thus potentially leading to lower CNS serotonin levels in winter.

To sum up our findings concerning serotonin: the simple measurement of WB-5HT (even if repeated) is unlikely to provide enough useful information in order to guide the clinician in the treatment of OCD. We set out to replicate previous findings (Thorén et al. 1980 b, Flament et al. 1987), acquired by invasive or technically more demanding methods. Nevertheless, those measurements probably merely represent reflections of the serotonergic action of SRIs that is enabling the clinical response; as opposed to measurements that are linked to the clinical response *per se*. Serotonergic measurements in peripheral blood (arguably also CSF serotonergic measurements) may then be equivalent to the measurement of medication compliance. That is, those measures may not inform on salient events within the brain that mediate the clinical response; rather they inform on the compartmental bioavailability of the medication. An international consensus project (Bandelow et al. 2016 b) recently concluded that "none of the putative biomarkers is sufficient and specific as a diagnostic tool". They also stated that "the most robust evidence for an involvement of serotonin derives from the fact that a large number of drugs that are effective in

anxiety disorders, OCD and PTSD have a common denominator, i.e., that they have an impact on serotonergic neurotransmission."

### 6.1.3 Peripheral measurement of oxytocin in OCD (papers IV-V)

#### 6.1.3.1 Summary of our oxytocin findings

Oxytocinergic mechanisms in OCD constitute an insufficiently researched field. Generally, few studies are at hand, and their findings are sometimes contradictory and difficult to interpret. I will discuss them in their context in the following. Our two main findings concerning oxytocin in relation to OCD were: 1) a positive correlation between plasma oxytocin levels and severity of OCD in the untreated patients at baseline, and 2) the markedly different trajectories of plasma oxytocin in SRI responders compared to SRI non-responders. These findings are difficult to reconcile with a simple mechanistic model, and there is a shortage of similar research to compare with. However, the fact that our trial included a placebo-treated control group enabled two further findings concerning the effects of SRIs *per se* on the oxytocinergic system (conceivably independent of the diagnosis of those treated). These findings were: 3) no net effect on plasma oxytocin of SRI treatment at a group level after 4 weeks, and 4) an association between delayed orgasm and increase of plasma oxytocin. These findings each warrant a more detailed discussion.

#### 6.1.3.2 Correlation between oxytocin levels and OCD severity

We found a positive correlation between baseline plasma oxytocin and the Y-BOCS scores of our untreated OCD patients. In fact, this is a replication of the first study on this matter, presented by Leckman et al. (1994 a). These investigators included 29 OCD patients aged between 18 and 61 years (mean 34 ± 13) with mean Y-BOCS score 24.1 ± 7.4, as compared to our 36 patients aged between 18 and 74 (41 ± 13) and with Y-BOCS of 25.7 ± 5.0. However, the most important difference between our studies is probably that they analysed oxytocin in CSF while we analysed it in plasma. In spite of this, the correlations between oxytocin and OCD severity were strikingly similar between our studies, except that Leckman's group found this correlation only among their "pure" OCD patients (i.e. those without tics, n = 19). Furthermore, the non-tic OCD cases also had higher oxytocin than a group of healthy controls. Leckman et al. argue that these findings support partly separate aetiologies for OCD with or without tics.

In our 36 patients, we found no difference between the clinically identified subtypes of OCD (see *Figure 4*), however, the correlation (oxytocin/severity) that we found in untreated patients, was clearly confined to those OCD patients that later responded to SRI. The correlation in future SRI responders and the lack of correlation in SRI non-responders may be interpreted as support for a "neuroendocrine" OCD subtype, where elevated oxytocin is involved, and which may predict SRI response.

There is a second previous study of CSF-oxytocin in OCD patients (Altemus et al. 1999). In this study, only 14 patients with OCD had their CSF-oxytocin levels measured, but they were compared to 26 healthy controls. OCD patients had numerically higher CSF-oxytocin, but the difference did not reach statistical significance. Additionally, in this small study, no correlation between oxytocin levels and OCD severity emerged. It seems reasonable to assume that the lack of findings in this study is related to the small sample size. Given that Leckman's significant correlation (CSF-oxytocin *vs* Y-BOCS score) is based on 19 OCD patients and our very similar correlation (paper IV) is based on 36 patients, we think that these findings, taken together, support the notion of a link between oxytocin and OCD.

#### 6.1.3.3 Changes of oxytocin related to anti-obsessive response

We have shown highly significant correlations between dynamic changes of plasma oxytocin during the first four weeks of SRI treatment and subsequent clinical improvement of OCD. This correlation was most pronounced for the range of oxytocin changes: those patients whose oxytocin varied most were also those most improved on all OCD severity measures.

#### 6.1.3.4 Effect of SRI treatment on oxytocin in humans

Concerning the effect of SRIs *per se* on the oxytocinergic system, our study appears to constitute the first controlled study in human subjects documenting the effect of any antidepressant treatment on oxytocin measurements. In contrast to the abundant availability of rodent studies on this topic, we only managed to identify three previous human studies on oxytocin changes in relation to antidepressant treatment, and none of them included a comparison with placebo treatment.

In the first of these, Altemus et al. (1994) analysed oxytocin in the CSF of 16 children/adolescents with OCD, before and after a flexible duration of clomipramine treatment. After clomipramine treatment, ranging between 8.5 and 34 months, there was an overall increase of mean CSF oxy-

tocin by 11%, a significant increase only if values were age-corrected. Paradoxically, however, the individual clinical response correlated negatively to CSF oxytocin changes, i.e. those with the least increase of CSF oxytocin were the most improved. Among the responders in our study, oxytocin initially decreased and later increased in plasma, possibly the result of gradual changes of the regulation of oxytocinergic transmission. Changes in opposite directions could imply that separate neuron populations are differently regulated. It should be noted that both plasma and CSF oxytocin concentrations mainly depend on the release of oxytocin from the magnocellular neurosecretory cells in the paraventricular (PVN) and supraoptic (SON) nuclei, while intracerebral synaptic transmission of oxytocin is derived from other types of hypothalamic neurons. Reasonably, this intracerebral synaptic transmission is more likely to have an impact on obsessive-compulsive symptoms, as compared to the peripheral plasma levels. Unfortunately, the mechanisms involved in regulation of different oxytonergic circuits are poorly understood. Accordingly, it is conceivable that oxytocin release in peripheral blood may increase in parallel with a decrease of intracerebral synaptic oxytocin. If this were the case, it could explain the paradoxical finding by Altemus et al. (1994).

In the next study (Ozsoy et al. 2009), the investigators measured plasma oxytocin in 40 patients with major depression before and after successful treatment, which was SRIs (venlafaxine or SSRI) in 19 cases. When compared to a control group, these depressed patients had significantly lower plasma oxytocin at baseline, but there was no difference between the patients' pre-treatment and post-treatment oxytocin levels. All patients included in the study were treatment responders, and the authors did not communicate the time interval between samples.

More recently, a third study (Keating et al. 2013) reported on plasma oxytocin at baseline and after 12 weeks' treatment in 16 adult patients with major depressive disorder; they were all treated with SSRIs and only responders were included. The authors found no difference between pre- and post-treatment plasma oxytocin levels.

To summarise these previous three studies, none of them used placebo-treated patients as control, nor did they compare responders to non-responders. One of them investigated patients with OCD (Altemus et al. 1994) and the other two dealt with depressive patients. Only one (Keating et al. 2013) applied a fixed time interval for the second oxytocin sample. Only the OCD study (Altemus et al. 1994) showed a significant change (increase) of oxytocin. This study measured oxytocin in CSF, but since it

only included treatment responders and did not compare their clomipramine treated patients with a placebo group, it is not possible to draw conclusions on the pharmacological effects of clomipramine *per se* on the oxytocin system. The changes could e.g. be secondary to the changes of life style resulting from long-term anti-obsessive response. Moreover, the long and variable time interval between pre-treatment and post-treatment samples, make the evaluation of temporal evolution very difficult.

In our study, we found no difference of oxytocin evolution over time when we compared all the SRI treated with all the placebo treated subjects. This null finding could be due to the limited sample size or other methodological factors. However, this result is more likely to reflect a marked individual variability regarding the reactivity of the oxytocinergic system, due to e.g. genetic, developmental or environmental factors. In support of this, there was a correlation between the age at OCD onset and the pre-treatment oxytocin level; furthermore, the individuals with autistic traits had significantly lower intra-individual oxytocin range compared to the other patients. Hypothetically, a compromised development of the capacity of hypothalamic oxytocinergic neurons may result in a restricted intra-individual oxytocin range among those with autistic traits. This hypothesis is well in line with recent research conducted within the field of autism neurobiology (Insel et al. 1999, Dölen 2015).

#### 6.1.3.5 Oxytocin and sexual side effects

Our study was, to our knowledge, the first to examine SRI induced sexual side effects in relation to oxytocin in humans. Contrary to expectations, delayed orgasm was related to higher plasma levels of oxytocin, while the SRI concentrations were unrelated. Thus, our results suggest that oxytocin levels have greater importance on orgasmic function than the concentration of the drug in serum. In previous research based on rat studies (de Jong et al. 2007), oxytocin was hypothesised to facilitate orgasm in SSRI-treated individuals. During the years that have passed since then, however, not a single human case report in support of this has appeared. Furthermore, a recent study of an oxytocin antagonist for premature ejaculation in men failed to show any significant effect (Shinghal et al. 2013), which aligns well with our findings. In summary, previous suggestions that oxytocin may counteract sexual side effects of SRIs are unlikely to be useful in humans.

## 6.2 Strengths and limitations of the presented results

### 6.2.1 BOCS study (paper I)

In this study, we used a large and rather disparate group of psychiatric outpatients for our psychometric tests. As opposed to most other validations of OCD rating scales, we compared the rating results of OCD patients with other types of psychiatric patients instead of healthy controls. This may limit the possibilities to compare our results with those of other OCD scales; however, it strengthens the evidence for clinical utility of BOCS. In addition, as several of the OCD patients were treated for their OCD at the time of the study, they scored lower than they would have done prior to treatment. This suggests that the sensitivity and specificity of the Severity Scale would have been even higher, if tested in treatment naïve OCD subjects. One important limitation is that the sensitivity to change during treatment of BOCS scores was tested in only 12 patients. This needs further studies.

In a clinical context, it is of importance that screening instruments have a predictive value among the everyday mixture of all kinds of psychiatric complaints, where healthy subjects are rare. Accordingly, although there is a competition among self-rating instruments for OCD, the BOCS has qualities that may out-perform a number of its competitors.

### 6.2.2 Serotonin and oxytocin studies (papers II-V)

One major strength of these studies is that the patients were followed-up for several years by one interested clinician (Susanne Bejerot) that assessed them for several additional measures, including personality and autistic traits, diagnostic subtypes and symptom dimensions. This had the result that we were able to exclude two patients that were originally included in the PXOS trial. These patients had erroneously been diagnosed as OCD, but did not fulfil the diagnostic criteria and suffered from other problems. As opposed to most of the later pharmaceutical industry sponsored multicentre trials, at the time of this trial, we were allowed to include additional tests. Considering that repeated measures of biochemistry at more than two time points are rare in human psychopharmacology, the thrice-repeated measurements in papers II-V is another strength. E.g., the markedly different trajectories of oxytocin levels between the SRI responders and all the non-responders in paper IV would not have appeared, if we had not included an oxytocin sample after one week of treatment.

Major limitations are the small sample size and lack of a control group of healthy subjects, which would have increased the possibilities to draw conclusions on the role of oxytocin in OCD.

### 6.2.3 Oxytocin studies (papers IV-V)

A major strength of these studies is that they still constitute the first clinical studies were plasma oxytocin has been measured repeatedly in psychiatric patients. Research on oxytocin has advanced considerably since we started our work in the field. Among the most debated disagreements are the neuroendocrine validity of intranasal challenges/treatments with oxytocin (Leng & Ludwig 2016) and the reliability of plasma oxytocin measurements (Szeto et al. 2011, McCullough et al. 2013). In our study, we did not use intranasal challenge or treatment, and the method we used for measuring plasma oxytocin, including plasma extraction, belongs to the most reliable type of methods for measuring plasma oxytocin (Szeto et al. 2011).

On the other hand, oxytocin may increase in a pulsatile way, why repeated samples on each sample day are preferable; however, we only took single samples. The small sample size in both these studies is a major shortcoming, limiting the possibilities to draw conclusions from these findings. Since we conceived these studies as explorative, the need for replication was expected. Accordingly, we believe that future studies in these fields are likely to become more fruitful if they base their design on information from our findings.

## 6.3 Hypothetical neurochemical model of OCD

### 6.3.1 The role of serotonin

Exhaustive and laborious research from 1980 until the present has largely failed to identify a primary disturbance of the serotonergic system (see 1.5.3.1.4). Yet, the only psychopharmacological principle that has been consistently linked to anti-obsessive efficacy is potent inhibition of the transporter protein of serotonin (serotonin reuptake inhibition). A reasonable conclusion from this paradox is that serotonin is crucially involved in the positive effect of SRIs, not because the treatment normalises a primary disturbance of serotonin, but because this manipulation of serotonin secondarily affects other CNS mechanisms. These other mechanisms, then, should be more convincingly linked to the pathophysiology behind the emergence of obsessive-compulsive symptoms.

The question is what are those other mechanisms?

### 6.3.2 A proposed neuroendocrine subtype of OCD

Researchers have repeatedly concluded that OCD is a heterogeneous disorder. Subtyping attempts have succeeded each other. Based on comorbidity patterns, reasonable groups are autism-spectrum related subtype, tic-disorder related subtype, anxiety-related subtype, affective-disorder related subtype and psychosis-related subtype. Based on known aetiological factors (somewhat related to age at onset), an early onset inflammatory subtype and a usually late onset lesion-related subtype emerge. Then, however, a rather large group remains, without conspicuous neuro-inflammatory or organic, brain injury features, without tics, psychotic or autistic traits, and usually with a post-puberty onset. These individuals may form the group where neuro-endocrine mechanisms contribute in a more crucial way as aetiological and pathophysiological factors. Gonadal hormones are likely to be of importance (Eriksson 2007), but our work may have revitalised the previously expressed notion (Leckman et al. 1994 b) that oxytocin may be involved in OCD pathophysiology. Since that time, numerous studies have indicated close interactions between the serotonergic and the oxytocinergic systems (Uvnäs-Moberg et al. 1999, Jørgensen et al. 2003, Emiliano et al. 2007, Yosida et al. 2009, Mottolese et al. 2014). As recently reviewed (Uvnäs-Moberg et al. 2015), oxytocinergic parvocellular neurons emanating from the paraventricular nucleus (PVN) project to many of the brain's most important structures and nuclei, regulating emotions, social interaction and stress reactions. Hypothetically, a variant wiring of this system may have an increased potential to give rise to obsessive-compulsive phenomena when activated by oxytocin. This can explain the increased incidence of OCD in the post-partum period (Russell et al. 2013), and is supported by animal experiments on grooming behaviour (Marroni et al. 2007). Many other transmitters are likely to be involved, but the hypothesis of a central role of oxytocin may be tested, e.g. by studying the effects of oxytocin antagonists on OCD-related mechanisms.

## 6.4 Potential clinical and scientific contributions

For the clinical management of OCD, the most important contribution from our studies is undoubtedly the work with the rating scale BOCS, presented in paper I. Clinicians and other therapists now have free access to a validated, user-friendly rating instrument for OCD.[13] The BOCS is

[13] Both the Swedish and the English versions of the BOCS scale can be downloaded at: http://memogen.se/tests.html

suitable for diagnostic assessments as well as for treatment monitoring (however, its sensitivity to change needs further study), and as self-rating questionnaire as well as for clinician rating. Importantly, it is simpler and less time-consuming than available alternatives.

For psychiatric pharmacotherapists, however, the clinically applicable results of our ambition to find simple biochemical markers, guiding the treatment, may seem unimpressive. The former hegemony of the serotonin hypothesis of OCD inspired us to test whether we could replicate, in a clinically more feasible setting, the promising previous results (Thorén et al. 1980 b, Flament et al. 1987), indicating the usefulness of serotonin-related measurements. Our unexpected opposite result (paper II-III) should not be interpreted as an invalidation of the importance of serotonin, since it remains well-proven facts that SRIs constitute effective treatments for many patients with OCD and that serotonin is crucially involved in their mechanism of action. However, our study reinforces the impression that non-response to SRIs is unrelated to the bioavailability of these drugs, and that other factors may be more important. As briefly mentioned in paper III, inflammatory factors are likely relevant in this respect. Incidentally, our method of measuring serotonin turned out to inform, indirectly, on inflammatory factors. Presently, however, psychiatric research is more whole-heartedly focussing on such factors, why better methods are available, directly addressing inflammation and immunological mechanisms. Thus, while not clinically applicable in the way we intended, our findings on serotonin validate the present efforts to delineate inflammatory-immunological involvement in OCD (Swedo et al. 2012, Rao et al. 2015, Shalbafan et al. 2015) as well as in other psychiatric disorders.

Similarly, our work with oxytocin was also unable to generate methods that can presently be helpful in clinical praxis. More research is necessary to disentangle the role of oxytocin in OCD. The suggestion that sexual side effects in men during SRI treatment predict a positive response may encourage the patient to continue the treatment, in spite of this side effect. Seemingly, serotonin measurements from peripheral blood or from the CSF are merely confirmation of patient compliance with taking the drug. However, we have probably contributed to some improvement of the clinical management of OCD patients, and possibly also to some details of the understanding of SRI mechanisms. Our findings clearly indicate that in the scientific discussion of the neurochemical pathophysiology of OCD, oxytocin should not be over-looked.

## 6.5 Future research

### 6.5.1 Oxytocin and OCD

Some interesting avenues have opened up in recent oxytocin research.

It has been shown that nicotine activates oxytocin through hypothalamic neurons in the PVN (Bisset & Walker 1957, Mikkelsen et al. 2012). It has also repeatedly been shown that patients with clinical OCD smoke significantly less than patients with other psychiatric diagnoses and also less than the general population (Bejerot & Humble 1999, Sharma et al. 2012, Abramovitch et al. 2015). If oxytocin is involved in this smoking disparity, and depending on how the data on oxytocin and OCD are interpreted, this may indicate either that OCD patients avoid activities that aggravate their symptoms (if oxytocin aggravates OCD) or would improve in their OCD symptoms from nicotine administration (if endogenously produced oxytocin ameliorates OCD). Obviously, these alternative hypotheses could be empirically tested in clinical studies of OCD patients. Interestingly, based on the glutamate hypothesis of OCD, Lundberg and collaborators (2004) have already published a study of nicotine treatment in OCD. However, this was not a controlled study, including only 5 patients, why more research is necessary. In future studies on the effect of nicotine in OCD, inclusion of oxytocin related measures might concurrently provide useful information on the relation between OCD and oxytocin.

A recent study investigated the effect of ECT on symptoms of autism in an inbred mouse strain with autism-like phenotype (Hagen et al. 2015). Interestingly, a positive effect on core symptoms of autism was shown, but an oxytocin antagonist almost abolished the effect of ECT, implying that activation of oxytocin had mediated these positive effects. This could possibly explain the difference in treatment result in autism and OCD.

Unfortunately, our findings cannot determine whether improvement of OCD is associated with increased or decreased oxytocinergic transmission in relevant parts of the brain. However, two placebo-controlled studies of oxytocin treatment in OCD patients both failed to show any effect of this treatment, intended to increase the oxytocinergic transmission (den Boer & Westenberg 1992, Epperson et al. 1996). In view of this, future studies should consider to test the reverse, i.e. whether *decreased* oxytocinergic transmission would benefit OCD patients. One oxytocin antagonist, epelsiban, was recently tested in men with premature ejaculation (Shinghal et al. 2013) and was found ineffective, possibly due to the mainly peripheral

activity of this drug.[14] Obviously, when testing the possible benefits of an antioxytocinergic treatment in OCD, the use of a centrally active oxytocin antagonist should be mandatory. Such studies are likely to provide a better understanding of the role of oxytocin in the mechanisms behind OCD and, possibly, to identify novel targets for helpful psychopharmacological treatments of this disabling disorder.

## 6.6 Conclusions

The previous focus to find biochemical markers in OCD related to the serotonergic system has generally proven unsuccessful, especially when it comes to clinically useful markers, capable of guiding the diagnosing and treating clinician. Nevertheless, treatment with SRIs is helpful, and their frequently reported sexual side effects, specifically delayed ejaculation, seem to predict treatment response.

In spite of all the intense research on neurobiology of OCD, this common disorder remains an enigma concerning both aetiology and pathophysiology. Important contributions from imaging studies have clarified the anatomy of the neuro-circuits involved to some extent, but the driving force behind their abnormal activity is still undefined. The heterogeneity of OCD patients suggests that several alternative mechanisms via separate routes lead to a final common pathway, triggering the symptoms. Some of these alternative mechanisms are likely to operate in the putative neuroendocrine subtype of OCD, where oxytocin may play a role.

Since patients with OCD tend to be reluctant to disclose their symptoms, a more practicable rating tool such as BOCS is useful for identifying OCD, thus enabling successful treatment.

[14] On the other hand, as discussed in paper V, the result of the study by Shinghal et al. may also be explained as concurring with our results in paper V, i.e. in support of the hypothesis that oxytocin does not facilitate ejaculation in humans.

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# Sammanfattning på svenska (Swedish summary)

**Bakgrund:** Tvångssyndrom (*obsessive-compulsive disorder*, OCD) är en psykiatrisk åkomma som varierar i svårighetsgrad och kliniskt förlopp, där de svåraste fallen hör till psykiatrins mest invalidiserade och samtidigt mest svårbehandlade patienter. Med en prevalens mellan 1 och 2 procent, och många gånger en debutålder före pubertet, utgör tvångssyndrom en betydande del av befolkningens psykiatriska sjukdomsbörda, med ibland svår nedsättning av funktion och livskvalitet. Personer med tvångssyndrom är ofta hemlighetsfulla kring sina symptom (bl.a. p.g.a. skamkänslor), vilket försvårar klinisk identifiering och medför att många går obehandlade. Därför behöver man utveckla diagnostiska metoder som kan fånga upp dessa patienter inom såväl primärvård som psykiatri, inte minst därför att aktiv behandling i många fall kan göra stor skillnad vad gäller patienternas funktion och livskvalitet.

Psykofarmaka ingår ofta i framgångsrik behandling av OCD, men har också sina problem: Det tar lång tid innan förbättringen kommer tillstånd och kan avläsas. En ganska stor andel patienter svarar inte på läkemedelsbehandling, och det finns ingen effektiv metod att förutsäga vilka som kommer att dra nytta av den. Det är oklart varför bara serotoninupptagshämmande antidepressiva läkemedel (SRI) har säkerställd effekt vid tvångssyndrom, trots att man inte har kunnat påvisa någon tydlig avvikelse inom serotoninsystemet hos drabbade individer. Dessutom kan serotoninupptagshämmare orsaka biverkningar, varvid sexuella funktionsförändringar hör till de vanligaste. Det är dock fortfarande oklart hur serotoninupptagshämmarna bidrar till sexuella biverkningar.

**Syften:** Det ena syftet med förestående avhandling var att undersöka användbarheten av en kortfattad skattningsskala,”Brief Obsessive Compulsive Scale” (BOCS) bland psykiatriska öppenvårdspatienter, där samsjuklighet med andra psykiatriska tillstånd kan försvåra diagnostiken.

Det andra syftet var att undersöka vissa biokemiska markörer hos patienter med OCD som behandlas med SRI, för att studera om dessa markörer uppvisar några samband med patienternas behandlingsrespons och sexuella biverkningar, samt om dessa eventuella samband skulle kunna bidra med information om sjukdomsmekanismer vid OCD.

**Skattningsskalan:** BOCS är en förkortad och bearbetad version av ett väletablerat men tungarbetat skattningsformulär, Yale-Brown Obsessive Compulsive Scale (Y-BOCS). BOCS består av tre olika delar: en checklista som kartlägger förekomst av olika symptom, en uppskattning av fördelningen mellan tvångstankar och tvångshandlingar samt en mätning av svårighetsgrad. Checklistan innefattar 14 tvångssymtomrelaterade frågor och en fråga som berör självskadande beteende. Denna del kan i regel användas som självskattningsformulär. Mätningen av svårighetsgrad omfattar 6 frågor. Denna del av skattningen genomförs med fördel tillsammans med en kliniker.

Vi genomförde en psykometrisk testning av BOCS genom att samla in skattningsresultat från 402 noggrant diagnostiserade patienter med varierande psykiatriska diagnoser, varav 94 hade primär OCD-diagnos. I studien har vi kunnat visa att BOCS har en god förmåga att identifiera och särskilja patienter med OCD bland patienter som lider av andra psykiatriska tillstånd. I en faktoranalys har vi också visat att BOCS fångar upp de viktigaste symptomvarianterna av OCD och även några besläktade tillstånd. BOCS används redan nu i stor utsträckning på psykiatriska kliniker, dels som ett screening-instrument för OCD-relaterade tillstånd, dels som ett stöd för kliniker att diagnostisera OCD, samt även för att följa behandlingseffekt vid behandling av OCD. BOCS är fritt tillgänglig för nedladdning från: memogen.se/tests.html

**Den biokemiska studien:** Under 1990-talet genomfördes ett flertal multinationella behandlingsstudier med selektiva SRI (SSRI) på vuxna med OCD. Vi deltog i en av dessa, en randomiserad, dubbelblind, placebokontrollerad studie av det på den tiden nya SSRI-preparatet paroxetin. Effekt och biverkningar av paroxetin jämfördes i studien dels mot det redan då etablerade SRI-preparatet klomipramin och dels mot placebo. Vi använde oss av denna studie för att kunna genomföra vår biokemiska studie, vilket medförde fördelen att vi kunde jämföra SRI-preparatens effekter med effekten av placebo-behandling. Hormonet oxytocin i plasma och signalsubstansen serotonin i helblod mättes i blodprover från 36 av patienterna vid flera tidpunkter under behandlingens gång (före behandlingsstart och efter 1 och 4 veckors behandling). Vi undersökte sedan hur dessa mätvärden förhöll sig till svårighetsgrad och behandlingsrespons efter 12 veckors behandling, samt hur de förhöll sig till graden av sexuella biverkningar efter 6 veckors behandling.

**Serotoninets betydelse:** Vi fann att serotoninnivåerna i blod under studiens gång sjönk med kraftigt varierande hastighet bland de SRI-behandlade patienterna medan de förblev oförändrade hos placebo-behandlade patienter. De SRI-behandlade som uppvisade en långsammare minskning av serotonin förbättrades vad gäller symptom på OCD i högre omfattning än de som hade en snabb minskning ($r = -0.61$, $p = 0.0006$).

Det är osannolikt att detta samband avspeglar förändringar av serotoninsystemet i hjärnan, men hypotetiskt kan sambandet ha en koppling till hastigheten i omsättningen av trombocyter (som lagrar serotonin i blodet). Detta skulle i sin tur kunna utgöra en koppling till inflammatoriska tillstånd som man vet kan påverka både trombocyter och neuropsykiatriska symptom. En samtidig förekomst av depression, tidigare behandlingsförsök av OCD och autistiska personlighetsdrag var också förenade med ett sämre behandlingsresultat.

**Oxytocinets betydelse:** Vi fann att högre oxytocin-nivåer i plasma i utgångsläget (före behandling) var relaterade till svårare OCD (mätt med Y-BOCS), men sambandet förelåg bara hos dem som senare faktiskt förbättrades av behandlingen med SRI. Oxytocin-nivåernas förändring hade ett motsatt mönster hos dem som förbättrades av SRI i relation till dem som inte förbättrades. De som inte förbättrades av SRI hade samma mönster oxytocin-förändring som de som inte förbättrades av placebo. Patienter som hade insjuknat i OCD tidigare i livet hade högre oxytocin-nivåer än de som insjuknat senare. Fördröjd orgasm var relaterat till högre oxytocinnivåer och till bättre behandlingssvar hos SRI-behandlade män. Ju mer oxytocin-nivåerna varierade hos SRI-behandlade individer, desto bättre blev behandlingssvaret, talande för att läkemedlens serotonerga mekanismer kan påverka oxytocinsystemet så att detta bidrar till förbättringen av tvångssyndrom. Våra studier kan bidra till ett underlag för att testa nya behandlingsformer för OCD, som ger en mer direkt inverkan på oxytocinsystemet.

# Appendix I: The BOCS, Swedish version



# BOCS
# Brief Obsessive Compulsive Scale

Av S Bejerot. Baserad på YALE- BROWN OBSESSIVE COMPULSIVE SCALE och CHILDREN'S YALE- BROWN OBSESSIVE COMPULSIVE SCALE

| | |
|---|---|
| Namn: | Födelsenummer: |
| Datum: | Bedömare: |

***Checklistan kan fyllas i av patienten själv (över 15 år), men yngre barn bör få checklistan uppläst. Frågorna på sid 4 bör värderas av klinikern i en intervju.***

”Tvångstankar" och "Tvångshandlingar" kan förklaras på följande vis:

”**Tvångstankar**” är störande tankar, idéer, en känsla, fantasier, inre bilder eller impulser som återkommer i dina tankar fastän du skulle vilja slippa dem. Eftersom tvångstankarna leder till obehag brukar man göra tvångshandlingar för att minska obehaget.

”**Tvångshandlingar**” är, å andra sidan, ritualer eller vissa handlingar som du känner dig pressad att utföra, även om du kanske vet att de är orimliga eller överdrivna. Ibland försöker du kanske att sluta att göra dem, men det kan vara alldeles omöjligt. De flesta tvångshandlingar är beteenden som syns, men vissa tvångshandlingar pågår bara i ens eget huvud, till exempel tysta kontroller eller ett behov av att upprepa vissa ord för sig själv varje gång man tänkt en störande tanke.

Markera de symtom som besvärar dig *just nu* (senaste veckan) med ett **X** i rutan ”Nu”. Om de har förekommit tidigare, men inte nu längre, markera dem med ett **X** i rutan ”Tidigare”. Det finns exempel som hjälp för att bestämma om det som du har kan vara ett tvångssymtom. Har du aldrig haft ett symtom så ska du markera ett **X** i ”Aldrig” –rutan.

| **Smitta/Renlighet** | **Nu** | **Tidigare** | **Aldrig** |
|---|---|---|---|
| 1. Jag oroar mig för smuts, smitta, bakterier eller virus.<br>*Ex. Rädd för att få på sig bakterier, eller aids, genom att sitta på vissa stolar, säten, ta i hand eller ta på dörrhandtag.* | ☐ | ☐ | ☐ |
| 2. Jag tvättar mig överdrivet mycket eller på ett visst sätt för att slippa smitta eller föroreningar.<br>*Ex. Tvättar händerna många gånger om dagen eller alltför länge efter att ha berört eller trott sig ha berört något förorenat eller nedsmutsat föremål.* | ☐ | ☐ | ☐ |

| **Tvångstankar om att skada** | **Nu** | **Tidigare** | **Aldrig** |
|---|---|---|---|
| 3. Jag är rädd för att jag kan råka skada andra människor.<br>*Ex. Rädsla för att förgifta andras mat, rädsla för att skada spädbarn, rädsla för att knuffa någon framför tåget, rädsla för att förorsaka skada genom att ge felaktiga råd.* | ☐ | ☐ | ☐ |
| 4. Jag är rädd för att ett plötsligt infall ska få mig att göra något som jag inte vill.<br>*Ex. Rädd för att köra in i ett träd, rädd för att köra över någon, rädd för att sticka ned någon med kniv.* | ☐ | ☐ | ☐ |

**Sexuella tvångstankar** Dessa tankar skiljer sig från vanliga sexuella fantasier som ju istället upplevs som behagliga.

| | | | |
|---|---|---|---|
| 5. Jag har förbjudna eller perversa tankar eller inre bilder om sex, som känns obehagliga.<br>*Ex. Sexuella tankar, som man inte själv vill ha, och som handlar om främlingar, barn, familj eller vänner.* | ☐ | ☐ | ☐ |

**Kontroll**

| | | | |
|---|---|---|---|
| 6. Jag kontrollerar spisen eller andra elektriska apparater, att jag har låst eller att saker inte har försvunnit.<br>*Ex. Upprepade kontroller av dörrlås, spis, strykjärn eller eluttagen (kontakter) innan man går hemifrån; upprepade kontroller av att ens skåp i skolan är låst eller att man satt på sig sina kläder riktigt.* | ☐ | ☐ | ☐ |

**Religion/Magi/Vidskeplighet**

| | | | |
|---|---|---|---|
| 7. Jag oroar mig för att vanhelga eller häda, rädd för att förarga Gud eller vanhedra heliga ting.<br>*Ex. Oro för hädiska tankar, för att uttrycka sig hädiskt eller bli straffad för detta längre fram i livet eller efter döden.* | ☐ | ☐ | ☐ |
| 8. Jag måste göra vissa saker för att det känns som om jag då kan förhindra, på ett övernaturligt sätt, att något hemskt kan inträffa.<br>*Ex. Måste beröra saker eller personer, om man t.ex. berör en telefon (eller något liknande) får man en känsla av att man kan förhindra sjukdom i familjen.* | ☐ | ☐ | ☐ |

**Moral & Rättvisa**

| | | | |
|---|---|---|---|
| 9. Jag är överdrivet upptagen av vad som är rätt eller fel eller moralfrågor.<br>*Ex. Oro för att inte alltid göra "det rätta", att ha ljugit eller lurat någon.* | ☐ | ☐ | ☐ |

**Symmetri/Exakthet/Ordnande**

| | | | |
|---|---|---|---|
| 10. Jag har tvångstankar om att jag måste ha en viss ordning, symmetri, eller att det ska kännas exakt rätt (men det är inte kopplat till ett magiskt tänkande).<br>*Ex. Oroas över att papper och böcker inte är ordentligt staplade, oroas för att beräkningar eller handstilen inte är tillräckligt perfekt eller "att det inte ska gå jämt upp".* | ☐ | ☐ | ☐ |
| 11. Jag har ett tvång att ställa i ordning eller arrangera mina saker.<br>*Ex. Rättar till papper och pennor på skrivbordet eller böckerna i bokhyllan, ägnar mycket tid till att ställa saker "i ordning" och blir upprörd eller arg om denna ordning rubbas.* | ☐ | ☐ | ☐ |

| **Precis rätt/Upprepning/Räkna** | **Nu** | **Tidigare** | **Aldrig** |
|---|---|---|---|
| 12. Jag måste upprepa vissa handlingar tills de känns precis rätt.<br>*Ex. Upprepa beteenden som t.ex. att vrida av och på kranen, sätta på och stänga av apparater, kamma håret, gå fram och tillbaka över en tröskel.* | ☐ | ☐ | ☐ |
| **Samla & Spara** | | | |
| 14. Jag hamstrar och samlar saker.<br>*Ex. Sparar gamla tidningar, anteckningar, burkar, pappershanddukar och omslagspapper, av rädsla att om man kastar bort dem så kommer man en dag att behöva dem; tar med sig värdelösa saker från gatan.* | ☐ | ☐ | ☐ |
| **Kroppsliga tvångstankar** | | | |
| 15. Jag tänker överdrivet mycket på någon del av kroppen eller fixerar mig vid något i mitt utseende.<br>*Ex. Oro över att ansiktet, näsan, ögonen, eller någon annan del av kroppen är fasansfullt ful trots försäkringar om motsatsen.* | ☐ | ☐ | ☐ |
| **Självskadande beteende** | | | |
| 16. Jag skadar mig själv.<br>*Ex. River sig, drar loss hud, skär sig, bankar huvudet i väggen.* | ☐ | ☐ | ☐ |

**Tvångsproblem som du har, men som inte finns med på listan, kan du skriva ned här:**

1. _____
2. _____
3. _____

**Dina mest besvärande tvångsproblem kan du skriva ned här:**

1. _____
2. _____
3. _____

**Hur mycket av dina tvångsproblem är tvångstankar och hur mycket är tvångshandlingar?**
*Svara på **antingen** fråga* A eller B.

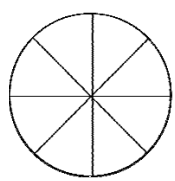
**A.** Försök att uppskatta procenten tvångstankar respektive tvångshandlingar, om de tillsammans blir 100%

**Tvångstankar: _____ %**
**Tvångshandlingar: _____ %**

**B.** Tvångstankarna och tvångshandlingarna ska tillsammans fylla hela cirkeln.
*Strecka antalet "tårtbitar" som utgörs av tvångshandlingar. De tårtbitar som du inte fyller i utgörs av tvångstankar som du har.*

☐ = Tvångstankar

▨ = Tvångshandlingar



| | |
|---|---|
| Namn: | Födelsenummer: |
| Datum: | Bedömare: |

*Referera specifikt till de aktuella tvångsproblemen (tvångstankar och tvångshandlingar).*
*Be patienten besvara frågorna utifrån hur det har varit de senaste **sju dagarna** (inklusive idag).*

***1.*** **Ungefär hur mycket tid upptas av dina tvångsproblem?**
0= Ingen.
1= Mindre än 1 timme om dagen eller något enstaka tvångssymtom.
2= 1-3 timmar om dagen eller ofta förekommande tvångssymtom.
3= Mer än 3 och upp till 8 timmar om dagen eller mycket ofta förekommande.
4= Mer än 8 timmar om dagen eller nästan konstant förekommande.

***2.*** **I genomsnitt, hur många vakna timmar i <u>sträck</u>, är du helt fri från tvångsproblemen, som mest?** (tim/dag)
0= Inga symtom.
1= Långt symtomfritt intervall, mer än 8 symtomfria timmar i sträck.
2= Medellångt symtomfritt intervall; mellan 3-8 symtomfria timmar i sträck.
3= Kort symtomfritt intervall; mellan 1-3 symtomfria timmar i sträck.
4= Extremt kort symtomfritt intervall, mindre än 1 symtomfri timme i sträck.

***3.*** **Hur mycket hindrar tvångsproblemen dig i din vardag, med arbete/skolgång och din förmåga att umgås med familj och vänner?**
0= Ingenting.
1= Liten; det hindrar till viss del sociala aktiviteter eller studier/yrkesliv, men den sammantagna prestationen är inte nedsatt.
2= Måttlig; definitivt hindrande för sociala aktiviteter eller studier/yrkesliv, men fortfarande överkomligt.
3= Starkt; orsakar betydande hinder för sociala aktiviteter eller studier/yrkesliv.
4= Extremt; total oförmåga.

***4.*** **Hur besvärad är du av dina tvångsproblem?**
0= Inte alls.
1= Lindrigt; inte så besvärad.
2= Måttligt; besvärad men fortfarande överkomligt.
3= Starkt; mycket plågad.
4= Extremt; nästan konstant och invalidiserande plåga.

***5.*** **Vilken förmåga har du att behärska dina tvångsproblem? Hur väl lyckas du stoppa eller avleda dem? Om du sällan försöker så tänk ändå på hur det brukar gå de sällsynta tillfällen då du försökt**.
(obs: *räkna inte med tvångstankar som stoppas genom att utföra ritualer).*
0= Fullständig behärskning.
1= God behärskning, lyckas vanligen stoppa/avleda tvångssymtomen med lite ansträngning/koncentration.
2= Måttlig behärskning, lyckas ibland stoppa/avleda tvångssymtomen men bara med svårighet.
3= Dålig behärskning, lyckas sällan stoppa/avleda tvångssymtomen, men de kan skjutas upp tillfälligt.
4= Ingen behärskning, är knappast förmögen att ens för en kort stund strunta i tvångstankarna eller avstå från att göra tvångshandlingar; kan inte ens skjuta upp dem tillfälligt.

***6.*** **Har du undvikit att göra något, åka någonstans eller att vara tillsammans med någon för att slippa ifrån dina tvångsproblem?**
0= Inget medvetet undvikande.
1= Lindrigt undvikande.
2= Måttligt; visst undvikande beteende är klart närvarande.
3= Allvarligt; mycket undvikande beteende och undvikandet är framträdande.
4= Extremt; mycket uttalat undvikande; gör nästan allt han/hon kan för att undvika att utlösa symtom.

**Tvångstankar:_____%**
**Tvångshandlingar:_____%**
*(utgå från frågan på sid 3)*

**BOCS POÄNG (summera fråga 1 - 6)** ☐

# Appendix II: The BOCS, English version



# BOCS
# Brief Obsessive Compulsive Scale

By S. Bejerot. Based on Wayne Goodman's YALE- BROWN OBSESSIVE COMPULSIVE SCALE and CHILDREN'S YALE- BROWN OBSESSIVE COMPULSIVE SCALE

| | |
|---|---|
| Name: | Patient ID: |
| Date: | Clinician: |

***The patient (>15 years) can complete the checklist as a self-rating procedure, while the information from younger children should be obtained by interview. The questions on page 4 are to be completed by the clinician in an interview setting.***

The terms "obsessions" and compulsions" may be described in the following way:

**"Obsessions"** are distressing **thoughts**, ideas, feelings, fantasies, images (pictures) or impulses that keep coming into your mind even though you do not want them to. Since obsessions cause distress, compulsions are readily carried out to reduce it.

**"Compulsions"** on the other hand, are **habits,** rituals or behaviors, you feel you have to do, although you may know that they do not make sense, or are excessive. At times you may try to stop from doing them, but this might not be possible. While most compulsions are observable behaviors, some compulsions may be hidden mental acts that go on in your head, such as silent checking, or repeating certain words to yourself each time you have disturbing thoughts.

Check the obsessions and compulsions that trouble you *right now* (during the past week) in the "current" box. If they have occurred previously but not any longer, check the box marked "Past". There are examples of each symptom to help you decide if you have an obsessive-compulsive symptom. If you never have had the obsession or compulsion, check the box marked "Never".

| **Contamination/Cleanness** | **Current** | **Past** | **Never** |
|---|---|---|---|
| 1. I am worried about dirt, germs, virus.<br>*Ex. Fear of getting germs from touching door handles or shaking hands or sitting in certain chairs or seats or fear of getting AIDS.* | ☐ | ☐ | ☐ |
| 2. I wash my hands very often or in a special way to be sure I am not dirty or contaminated.<br>*Ex. Washing one's hands many times a day or for long periods after touching, or thinking one has touched, a contaminated object.* | ☐ | ☐ | ☐ |

| **Harming obsessions** | **Current** | **Past** | **Never** |
|---|---|---|---|
| 3. I fear that my actions might harm others.<br>*Ex. Fear of poisoning other's food, fear of hurting babies, fear of pushing someone in front of a train, fear of causing harm by giving bad advice.* | ☐ | ☐ | ☐ |
| 4. I fear I will loose control and do something I don't want to do.<br>*Ex. Fear of driving into a tree, fear of running over somenoe, fear of stabbing someone.* | ☐ | ☐ | ☐ |
| **Sexual obsessions** | | | |
| 5. I have unpleasant forbidden or perverse sexual thoughts, images or impulses that frighten me.<br>*Ex. Unwanted bad sexual thoughts about strangers, family members, children or friends.* | ☐ | ☐ | ☐ |
| **Checking** | | | |
| 6. I must check the stove or other electrical appliances, that I have locked the door or make sure that things have not disappeared.<br>*Ex. Repeated checking of door locks, the stove, the iron or electrical outlets before leaving home; repeated checking that one's cupboard at school is locked, or if one is properly dressed.* | ☐ | ☐ | ☐ |
| **Religion/Magical thoughts/Superstition** | | | |
| 7. My dirty words, thoughts and curses directed towards God bothers me; I have a fear of offending God.<br>*Ex. Worries about being punished for such sins and thoughts now, later in life or after death.* | ☐ | ☐ | ☐ |
| 8. In order to prevent something terrible to happen I must have special thoughts or acts done in a special way.<br>*Ex. Touching an object like a telephone insures that someone in the family will not get sick.* | ☐ | ☐ | ☐ |
| **Morality & Justice** | | | |
| 9. I am occupied with morality issues, justice or what is right or wrong.<br>*Ex. worries about always doing "the right thing", having told a lie, or having cheated someone.* | ☐ | ☐ | ☐ |
| **Symmetry/Exactness/Ordering** | | | |
| 10. How things are placed or how they are positioned is important to me. It needs to feel "just right" (but isn't associated with magical thinking).<br>*Ex. Worries about papers and books being neatly placed, worries about calculations or handwriting being perfect or not evening up.* | ☐ | ☐ | ☐ |
| 11. I get a compelling urge to put my things in a special order.<br>*Ex. Straightening paper and pens on a desktop or books in a bookcase, wasting hours arranging or lining up things in the house in "order" and then becoming very upset if this order is disturbed.* | ☐ | ☐ | ☐ |

| **Just right/ Repeating rituals/ Counting** | **Current** | **Past** | **Never** |
|---|---|---|---|
| 12. I have a compelling urge to repeat certain actions until it feels just right.<br>*Ex. Repeating activities like turning the tap or appliances on and off, combing one's hair, going in and out of a doorway.* | ☐ | ☐ | ☐ |

**Hoarding & Saving**

| | | | |
|---|---|---|---|
| 14. I must follow strong impulses to collect and hoard things.<br>*Ex. Saving old newspapers, notes, cans, paper towels and wrappers for fear that if one throws them away one may some day need them; picking up useless objects from the street.* | ☐ | ☐ | ☐ |

**Somatic obsessions**

| | | | |
|---|---|---|---|
| 15. I have worries that I look peculiar; I am concerned that something is wrong with my looks.<br>*Ex. Worries that one's face, ears, nose, eyes, or another part of the body is hideously ugly, despite reassurance to the contrary.* | ☐ | ☐ | ☐ |

**Self-damaging behaviors**

| | | | |
|---|---|---|---|
| 16. I do things that injure my body.<br>*Ex. Scratching and tearing the skin, cut oneself or banging one's head.* | ☐ | ☐ | ☐ |

**If you have other obsessive-compulsive problems (*obsessions/thoughts*, *compulsions/habits)* that are not included in the checklist, enter them here:**

1. _____
2. _____
3. _____

**Mark *the most troublesome* obsessive-compulsive problems, and enter them here:**

1. _____
2. _____
3. _____

**What is worse, your obsessions or your compulsions?**

*Please respond to **either** question* A or B.

**A.** If you separate your obsessions and your compulsions, what percent are the former and what the latter?

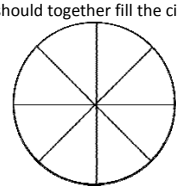
**Obsessions: _____ %**
**Compulsions: _____ %**

**B.** Obsessions and compulsions should together fill the circle.

*Please dash the sections that correspond to your compulsions/ habits. The empty sections correspond to your obsessions/thoughts.*

☐ = Obsessions/thoughts

▨ = Compulsions/habits



| | |
|---|---|
| Name: | Patient ID: |
| Date: | Clinician: |

*Review the current **obsessive-compulsive problems** (obsessions/thoughts and compulsions/habits).*
*Ask the patient to respond according to the situation during the last seven days (including today).*

1. **Approximately, how much of your time is occupied by obsessive-compulsive problems?**
   0= None.
   1= Occasional symptoms or less than one hour per day.
   2= Frequent obsessive-compulsive symptoms or1-3 hours per day.
   3= Very frequent symptoms or more than 3 and up to 8 hours a day.
   4= Almost constantly or more than 8 hours a day.

2. **On the average, what is the longest amount of consecutive waking hours per day that you are completely free of obsessive-compulsive problems? ___hrs/day.**
   0= No symptoms.
   1= Long symptom-free interval, more than 8 consecutive hours/day symptom-free.
   2= Moderately long symptom-free interval, more than 3 and up to 8 consecutive hours/day symptom-free.
   3= Short symptom-free interval, from 1 to 3 consecutive hours/day symptom-free.
   4= Extremely short symptom-free interval, less than 1 consecutive hour/day symptom-free.

3. **How much do your obsessive-compulsive problems interfere with your everyday life, work or school, or social functioning?**
   0= No interference.
   1= Mild; slight interference with social or occupational/school activities, but overall performance not impaired.
   2= Moderate; definite interference with social or occupational/school performance, but still manageable.
   3= Severe interference; causes substantial impairment in social or occupational/school performance.
   4= Extreme; incapacitating interference.

4. **How much distress do your obsessive-compulsive problems cause you?**
   0= None.
   1= Mild; not too disturbing.
   2= Moderate; disturbing, but still manageable.
   3= Severe; very disturbing distress.
   4= Extreme; near constant and disabling distress.

5. **How much control do you have over your obsessive-compulsive problems? How successful are you in stopping or diverting them? If you rarely try to resist, please think about those rare occasions on which you did try.**
   *(Note: Do not include here obsessions stopped by doing compulsions).*
   0= Complete control.
   1= Much control; usually able to stop or divert obsessive-compulsive problems with some effort/concentration.
   2= Moderate control, sometimes able to stop or divert obsessive-compulsive problems only with difficulty.
   3= Little control, rarely successful in stopping or dismissing obsessive-compulsive problems but they can be delayed for the moment.
   4= No control, are rarely able, even momentarily, to ignore obsessions or refrain from performing compulsions; they cannot even be delayed for the moment.

6. **Have you been avoiding doing anything, going anyplace or being with anyone in order to avoid your obsessive-compulsive problems?**
   0= No deliberate avoidance.
   1= Mild, minimal avoidance.
   2= Moderate, some avoidance; clearly present.
   3= Severe, much avoidance; avoidance prominent.
   4= Extreme, very extensive avoidance; patient does almost everything he/she can to avoid triggering symptoms.

**Obsessions:_____%**
**Compulsions:_____%**
*(refer to the question on page 3)*

**BOCS TOTAL (add items 1 - 6)** ☐

## Publications *in the series*
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