Obsessive Compulsive Disorder

Current Understanding and Future Directions

Until about two decades ago, obsessive-compulsive disorder (OCD) was considered an uncommon mental illness for which no effective treatment existed. Since then, there has been significant progress in the understanding and treatment of OCD. Recent developments in the field of neuroimaging, genetics and immunology have resulted in newer insights into this disorder. Learning and cognitive theories have contributed to specific treatment approaches. This book brings together some of the recent developments in the field and offers ideas to future research. The contributors to this book are well-known researchers in the area.

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Obsessive-Compulsive Disorder Current Understanding and Future Directions
Editors: Y C Janardhan Reddy, Shoba Srinath

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The symposium was held to commemorate completion of a decade of specialty OCD CLINIC at NIMHANS, Bangalore.

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Foreword

Obsessive-compulsive disorder (OCD) is a common and disabling mental disorder. It is twice as common as schizophrenia and bipolar disorder. OCD is largely underdiagnosed and inadequately treated. OCD mostly presents for the first time in adolescence and can thus incapacitate a person throughout his/her life. Despite its relatively early age at onset, only a minority of sufferers receive treatment early in the course of illness. OCD also has its relative share of stigma, resulting in long delays in treatment. This is compounded by the fact that most medical professionals are unfamiliar with its clinical characteristics resulting in delay in diagnosis and appropriate treatment.

Considerable progress has occurred in the last two decades in the treatment and understanding of this common psychiatric illness. Serotonin reuptake inhibitors and cognitive behavior therapy, both have improved the outcome of this illness, which was otherwise considered difficult to treat. There is also significant advance in the understanding of the neurobiology of OCD with respect to neural correlates of obsessional behavior, genetics and immunology.

However, despite the advances in understanding the neurobiology and the cognitive factors in the causation of OCD and availability of effective treatments, about 40% to 60% of the patients do not show satisfactory improvement. This shows that there is still much to be understood. This monograph brings together some of the latest developments in the understanding and treatment of OCD. The contributors to this monograph are well known researchers in the field, have put together a summary of the

latest developments in the field, and offer some fresh insights in to the future direction of research in the area.

This monograph is the proceedings of the symposium held in commemoration of completion of a decade of specialty OCD services at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore.

I hope this monograph serves as a useful reference source to all the mental health professionals involved in the care of persons suffering from OCD.

Dr. D. Nagaraja
Director & Vice-chancellor
NIMHANS

Preface

Considerable progress has occurred in the understanding and treatment of obsessive-compulsive disorder (OCD) in the last two decades. Serotonin reuptake inhibitors and cognitive behavior therapy have emerged as the mainstay of treatment in OCD replacing the ineffective and often long-drawn psychoanalytical treatment. There is considerable advancement in understanding the neurobiological basis of the disorder based on neuroimaging and neuropsychological studies. Genetic basis of the disorder is being explored vigorously. Immunological basis of the childhood OCD has received special attention from some researchers. In addition to these major advances in the field, there have been efforts in understanding OCD from the perspective of a spectrum concept. What is more, it is increasingly realized that OCD is perhaps not a unitary disorder. Researchers working with children point to the possibility of a developmental subtype of childhood OCD.

Despite the advances in the understanding and treatment of OCD and its improved prognosis, there are many areas of concern and disagreement among researchers. For example, some researchers try to understand the disorder entirely from a biological perspective and others from a cognitive and learning perspective. We are sure there must be a meeting point for researchers from diverse backgrounds and viewpoints. Of course, diverse viewpoints and disagreements often boost the efforts at better understanding and improve the quality of research. We know that 40 to 60% of the patients still do not show satisfactory response to treatment. All this implies that there is still much to be understood.

Several leading researchers in the area have contributed to this monograph. Their viewpoint and insight in to the nature of the disorder reflects to some extent at least the direction of the research in the area. The topics covered are most contemporary in the field and include diverse but related areas such as phenomenology, course and outcome, neurobiology, genetics, immunology and treatment of resistant OCD. The monograph also covers the role of psychotherapy in the treatment of OCD. There is an effort to understand the uniqueness of the disorder in children.

This monograph is a compilation of the proceedings of the international symposium held at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India on November 10 & 11, 2007. The symposium is being held to commemorate completion of a decade of specialty OCD services at the institute. The specialty OCD clinic was pioneered in 1997 by Dr. Sumant Khanna, a well-known clinician and researcher in the field. Although Dr Khanna's serious interest was in biological psychiatry and psychopharmacology, he is also largely responsible for popularizing the approaches of exposure and response prevention in treating OCD at our centre. He also collaborated with colleagues in child psychiatry to do some early work on the phenomenology of childhood OCD.

The OCD clinic at NIMHANS is very popular and caters to around 120 to 150 new patients per year and follows up close to 1000 patients in a year. Patients are often referred from across the country for management of resistant OCD.

This monograph is special for us for two important reasons. Firstly,

eminent researchers in the field have contributed to this monograph which enhances the authenticity of the issues discussed. Second, this monograph is symbolic of our obsession to provide specialized services to the sufferers of OCD and boost the research in the area. We hope the monograph serves as a useful reference to clinicians and researchers in the area.

Y C Janardhan Reddy
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Contents

Chapter 1

The Obsessive-Compulsive Spectrum of Disorders: Towards DSM-V and ICD-11

Dan J. Stein

There has been a good deal of interest in recent years in the concept of an obsessive-compulsive spectrum of disorders. Advances in the neurochemistry and neuroanatomy of Obsessive-Compulsive Disorder (OCD) have led to the question of whether disorders characterized by similar phenomenology and psychobiology are best conceptualized as OCD-related. This question is not merely a conceptual one; insofar as an OC spectrum construct would encourage more appropriate diagnosis and treatment of these putative OCD-related disorders, it would have important practical and clinical implications.

Much of the work on this debate has focused on data that emerges from family investigations, brain imaging research, and molecular genetic studies. In this paper, a conceptual approach is adopted, beginning with the question of what is a spectrum of disorders. A number of solutions are put forward, and then used to address some of the relevant psychobiological data.

From OCD to OCD Spectrum

At the start of the twentieth century, there were those who held that OCD was a rare disorder, caused by psychological conflicts, and poorly responsive to treatment. This century witnessed important advances in psychiatric

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diagnosis and epidemiology, in neuroimaging and molecular neuroscience, and in psychopharmacology and psychotherapy. By the end of the century, there was good evidence to suggest that OCD was a not uncommon disorder, that it was mediated by particular psychobiological mechanisms, and that it responded to both specific pharmacotherapies and psychotherapies (1).

Advances in OCD raised the question of whether conditions with similar phenomenology and psychobiology, would respond to pharmacotherapies and psychotherapies effective for OCD. Early work demonstrated that OCD responded more robustly to the serotonin reuptake inhibitor clomipramine than to the noradrenaline reuptake inhibitor desipramine. A range of investigators began to explore whether clomipramine was also more effective than desipramine in disorders such as body dysmorphic disorder, trichotillomania, as well as in various body-focused repetitive conditions and symptoms (2).

A narrow approach to defining the OCD spectrum has focused on disorders where there is significant psychobiological overlap with OCD. An early psychodynamic view was that OCD and related disorders were accounted for by similar defense mechanisms. More recent work has emphasized neurobiological overlap. Tourette's disorder is perhaps the OCD spectrum par excellence in this work, for it has a particularly close familial relationship with OCD (3). Moreover, within a particular family, irrespective of whether patients suffer from OCD or tics, they may have similar underlying abnormalities in brain imaging (4) suggesting a common endophenotype.

A broader approach to defining the OCD spectrum has included a much

larger number of disorders, ranging for example from those that are more compulsive (like OCD) to those that are more impulsive (5). In such a view, compulsive and impulsive traits can be seen in disorders that fall into a range of categories in standard classification symptoms. Examples of this would include disorders ordinarily diagnosed in childhood (such as Tourette's), in somatoform disorders (such as body dysmorphic disorder and hypochondriasis), in impulse control disorders (such as kleptomania, pathological gambling, and trichotillomania), and in eating disorders (such as anorexia and bulimia).

What is a Spectrum of Psychiatric Disorders?

It is useful to distinguish between two long-standing approaches to psychiatric classification (6, 7). A classical approach has emphasized the idea that psychiatric disorders are natural kinds, which can be defined in terms of their necessary and sufficient criteria. Just as a square can be defined as a figure with four equal sides at right angles, so a psychiatric disorder can be defined in terms of particular operational criteria. This approach has a venerable history; it draws on a long line of philosophical thinking about science, about language, and about medicine, and has had an important influence on contemporary psychiatric nosology.

A critical approach, on the other hand, has emphasized the idea that psychiatric disorders are socially constructed categories. Just as what is considered a weed reflects human practices that vary from time to time and place to place, so what counts as a psychiatric disorder says more about those who construct nosologies than about reality per se. This approach too has a long history; there are many who have argued that classical concepts of

science, language and medicine do not stand up to careful scrutiny, and this kind of thinking has had an important influence on contemporary critiques of psychiatric nosology.

From a classical perspective, two disorders fall on a spectrum if their necessary and sufficient criteria are closely related. Orange and red fall on a spectrum of light, precisely because they can be defined in terms of wavelengths of light which are very similar. From a critical perspective, the idea of putting two disorders on a spectrum mostly reflects sociopolitical machinations. If obsessive-compulsive disorder is taken out of the anxiety disorders, this may for example reflect that new drugs are available for OCD, and that the medical-industrial complex has chose to extend its power, by creating knowledge of and marketing for, the so-called OCD spectrum disorders.

It may be possible to construct an integrative approach to classification which is based on cognitive-affective science, and which goes beyond the classical and critical perspectives. The particular way in which our brain-minds are built means that there are a series of universal basic-level constructs that humans are familiar with. Pain, for example, is an experience that has existed across history and geography. However, our brain-minds are situated in a complex natural and social world, and so employ a range of more complex categories often based on metaphoric extension. Thus, many cultures might talk of the pain of losing a friend. Human categories have more central categories (eg. physical pain is a central example of pain, a robin is a typical bird) and more peripheral ones (eg., the loss of a friend is an atypical kind of pain, an ostrich is an atypical bird).

There is a broad range of scientific data in this area. Cognitive psychology has a rich empirical literature on prototypic categories (such as birds) (8). Artificial intelligence has built parallel distributed networks which model the graded nature of many categories (9). Linguistics has shown that many of our abstract concepts are structured using extensions of basic-level sensorimotor experience (10). Neuroscientists and anthropologists have explored categories such as color categories, and shown how these reflect both basic-level experience (eg. primary colors), but are extended differently in different languages (11). Developmental psychologists have shown how basic-level categories develop over time to cover more abstract phenomena (12).

Similarly, disorder is a prototypic but structured category. We cannot define disorder in an essentialist way, as our concepts of disorder emerge within our social practices (eg. in determining whether someone is distressed and impaired). At the same time, our categories of disorders are not simply wholly arbitrary or relativistic, they reflect particular extensions of basic-level experience, which can be more or less reasonable. Metaphors of disorder include those which structure disorder in terms of a pathway (eg. as suffering an impediment or a breakdown), a possession (eg. having attracted a contamination or an attack), or as an imbalance.

Thus, meningitis with decreased consciousness is a typical neuropsychiatric disorder; it can be structured using the metaphor of having a contamination, for which the patient has no responsibility, and deserves treatment. Substance abuse is a more atypical disorder, where we may reasonably use the idea of change brought by an external agent to argue that it is similarly structured to an infection, but where there may also be an acknowledgment of the agent's

responsibility for having developed the disorder, and where both treatment and increased responsibility for that treatment are required.

How does this approach conceptualize a spectrum of disorders? A first point would be that on a spectrum of psychiatric disorders, there are unlikely to be evenly spaced naturally cleaved division points (as there are on the light spectrum). Instead, some conditions are likely to be more central to the category, and others more peripheral or atypical. A second point would be that there is no single validator for configuring a nosology. Rather, any nosology reflects a broad range of considerations; these include both a number of different validators (each of which, if highlighted alone, might result in a somewhat different classification), as well considerations about clinical utility. In thinking about the OCD spectrum disorders, various aspects of clinical utility, can be considered this is discussed in detail in the next section.

Validation and Utility of the OCD Spectrum

A key validator of the OCD spectrum concept was mentioned earlier; the finding that a number of different disorders characterized by unwanted repetitive behavior responded more robustly to clomipramine than to desipramine. This finding perhaps fell on particularly receptive soil because it has immediate clinical utility. A range of disorders, which had previously been neglected, could now be effectively treated. Swedo and colleagues' work on clomipramine and desipramine in trichotillomania (13), for example, gave significant impetus to the birth of a whole range of studies on this disorder, many of them framed within the paradigm of exploring the obsessive-compulsive spectrum of disorders.

Nevertheless, it is notable that OCD and trichotillomania have many phenomenological and psychobiological differences. In direct contrast, although there is growing evidence that OCD and Tourette's involve a similar underlying endophenotype, perhaps a genetically mediated vulnerability to developing striatal dysfunction, these disorders are treated with different pharmacotherapies (serotonergic versus dopaminergic drugs) and psychotherapies (exposure vs. habit reversal therapies). Still there may be clinical utility in classifying OCD and TS together, for example, in encouraging assessment of tics in OCD, and OCD in TS.

The OCD spectrum concept has largely emerged from a biological psychiatry literature. The majority of this writing ignores the question of whether the functional analysis, in cognitive-behavioral terms, of symptoms in putative OCD spectrum disorders is similar or not. Certainly, a neuropsychiatric perspective on OCD has been valuable in encouraging exploration of underlying neurocircuitry and neurochemistry, as well as investigations of medications that act on these neurobiological mechanisms. At the same time, it is important not to neglect the possibility that higher level explanations may be crucial validators of the OCD spectrum concept, and that building such constructs into a classification system may have important clinical utility. Indeed, in deciding on what falls on the OCD spectrum, and how it should be configured, a whole range of sometimes conflicting findings must be weighed.

Cutting Edge of the OCD Spectrum

Given such considerations, in the near future it is not unlikely that OCD will remain conceptualized as an anxiety disorder. The complexity of nosological

decision-making should not, however, be equated with a sense of pessimism about future possibilities. Advances in our understanding of obsessive-compulsive disorder have certainly reinforced the possibility of a more conceptually rigorous and clinically useful classification system than that which existed in DSM-II and DSM-III. It can be speculated that advances in the cognitive-affective neuroscience of key cognitive-affective processes relevant to OCD, will ultimately lead to a better understanding of, and treatment approach to, both this disorder and putative OCD spectrum disorders.

One interesting possibility is concepts of OCD and spectrum disorders will emphasize reward processing more. Animal models and functional imaging have allowed the neurocircuitry of reward processing to be delineated, and show that the ventral striatum plays a key role (14). These methodologies have also provided data about the particular neurotransmitters involved in mediating the processing of rewards, dopamine plays a particularly important role (15). Such basic work has proved particularly relevant to understanding drug addiction; patients with substance use show abnormalities in the neurobiology of reward processing, and may respond to treatments acting on these pathways (16, 17).

One way of conceptualizing OCD is in terms of the absence of a feeling of goal completion after an action is performed; people continue with their compulsions repetitively until there is finally the sense that things are now just right. Furthermore, at the level of neurocircuitry, structural and functional imaging studies of OCD demonstrate that the ventral striatum plays an important role in mediating obsessive-compulsive symptoms (18) perhaps

disruption of this neurocircuitry underpins the failure of the signal that denotes goal completion. Finally, at a neurotransmitter level, dopamine is released in the ventral striatum under conditions of maximal uncertainty about subsequent reward, and also appears to plays a key role in mediating the symptoms of OCD (15), perhaps underpinning the sense of uncertainty about goal completion in OCD.

Reward processes are disrupted in a range of disorders, including mood disorders (19). A number of conditions involve repetitive goal-seeking behaviors; pathological gambling(PG) and hypersexual disorder, for example, may be characterized by disturbances in the processing of rewards (20, 21). Finally, Tourette's disorder, and stereotypic disorders such as trichotillomania, have also been described in terms of reward-deficiency by some authors (22). It turns out that in OCD patients, one cluster of putative comorbid OCD disorders comprises PG, hypersexual disorder, Tourette's, and trichotillomania (23), again raising the question of whether these diverse disorders share some underlying psychobiological features.

Of course, these various disorders, even if sometimes called 'compulsive', differ from OCD in key phenomenological and functional ways. PG, hypersexual disorder, and trichotillomania may involve a sense of pleasure at the time of the behavior, depression involves an inability to feel pleasure, whereas OCD is typically characterized by anxiety-inducing obsessions and anxiety-relieving compulsions. Perhaps different kinds of disturbances in reward processing result in a spectrum of diverse reward-related disorders. In terms of their underlying neurocircuitry, OCD is characterized by increased cortico-striatal activity, whereas PG, substance use disorders, and depression

tend to be associated with reduced orbitofrontal activity (17, 18). On the other hand, substance use disorders and OCD may both be characterized by low striatal D2 receptor availability (24, 17), and by glutamate dysfunction (25).

Conclusions

OCD is currently conceptualized as an anxiety disorder. Findings that various disorders have similar phenomenology and psychobiology, and sometimes respond to similar treatments, raise the question of whether to create a new category of OCD spectrum disorders in DSM-V and ICD-11. Many complexities remain in considering whether to configure such a new category, and if so then how best to do it. The analysis provides here on the nature of our constructs of disorder and of spectrums helps explain the nature of the many considerations that come into play. In the interim, the construct of an OCD spectrum has significant heuristic appeal, insofar as it encourages clinicians to screen for a range of neglected disorders, and to consider the use of potentially effective treatments that are also often ignored (2).

There is a good deal of evidence that OCD is characterized by disruptions in striatally and serotonergically mediated control processes (1). Such a view can potentially integrate a range of findings about compulsive and impulsive phenomena in OCD and related disorders, as well as about their underlying neurobiology. Thus, OCD is characterized by sudden intrusive symptoms, by inappropriate behavioral sequences, and by evidence of behavioral and cognitive disinhibition on neuropsychological testing (26), and perhaps increased frontal compensatory activity. In OCD, one cluster of comorbid OC spectrum disorders comprises intermittent explosive disorder,

kleptomania, eating disorders, and stereotypic self-injurious behaviors (23). In this view, compulsivity and impulsivity are not diametrically opposed, but rather may lie on orthogonal planes.

Future work on cognitive-affective processes relevant to OCD may ultimately result in a reconfiguration of the way in which we currently view the OCD spectrum of disorders. There is currently a good deal of excitement about advances in understanding reward processes, and the possibility that these may ultimately lead to a better way of conceptualizing and treatment these conditions. However, much additional work is needed in this area. Furthermore, it is quite possible that progress in other areas for example, understanding the psychobiology of disgust (27), may ultimately prove more important in addressing the question of whether the concept of OCD spectrum disorders is a valid one, and whether it has clinical utility in practice.

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Chapter 2

Is Obsessive-Compulsive Disorder a Unitary Disorder?

David Mataix-Cols and James F. Leckman

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (1) and other standard diagnostic classifications such as ICD-10 (2), regard ObsessiveCompulsive Disorder (OCD) as a unitary nosological entity. While this parsimony has a certain formal appeal, it is misleading. The symptoms used to define OCD are remarkably heterogeneous and two individuals with OCD may have totally different and nonoverlapping symptom patterns.

From as far back as the earliest descriptions of OCD, investigators have attempted to dissect the phenotype into homogeneous and mutually exclusive subtypes (Table1). For example, Falret made the distinction between *Folie du doute* (madness of doubt) and *Délire du toucher* (delusion of touch) in 1866. (4) With a few notable exceptions, such as the tic-related and early onset subtypes, these attempts had limited success in relating the identified subtypes to biological markers, genetic factors or treatment response. This was in part because pure subtypes of patients are rare, and the recruitment of sufficient sample sizes of each subtype is difficult and highly impractical (16-18).

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Table 1. Some attempts to classify obsessive-compulsive disorder patients into homogeneous, mutually exclusive subtypes.
Adapted from Mataix-Cols et al (17)

Obsessive-Compulsive Disorder Subtype	References
Folie du doute vs. *Délire du toucher*	3
Obsessions vs. compulsions	4
Primary obsessional slowness	5
Washers vs. checkers	6-9
Impulsive vs. non-impulsive	10
Early vs. late onset	11
Abnormal risk, pathologic doubt, incompleteness	12
Tic-like vs. no-tic-like	13
Primary vs. developmental	14
Autogenous vs. reactive obsessions	15

The following review considers an alternative dimensional approach to obsessivecompulsive (OC) symptoms that aims to identify valid quantitative dimensions for use in genetic, neurobiological, cognitive-behavioral and treatment outcome studies. The review then proceeds to examine the potential value of a dimensional approach from a developmental perspective. Finally, the results of a recent survey among international OCD experts and implications for the fifth edition of the DSM will be discussed.

Factor and Cluster Analytical Studies of OC Symptom Dimensions

Similar to phobias (19), there are a finite number of themes patients obsess

about and a corresponding limited range of ritualistic behaviors. From an evolutionary point of view, this suggests that obsessivecompulsive behaviors may have evolved to protect against particular kinds of threat (see discussion below). An increasing number of factor and cluster analytical studies of OCD symptoms support this idea. Mataix-Cols et al (16) recently summarized this literature and found strong evidence for at least four symptom dimensions, namely contamination/cleaning, hoarding, symmetry/order and obsessions/checking (Figure 1). Since publication of that review, at least eight large studies have been published replicating and further supporting this factor structure in adults with OCD (20-27). There is some controversy regarding whether or not that same dimensional structure is present in children and adolescents. Currently, three out of the four studies conducted in pediatric samples found evidence of a symptom structure largely congruent with that found in adults (28-31). The consistency in this literature is remarkable despite the use of different instruments (Yale Brown ObsessiveCompulsive Scale Symptom Checklist (YBOCS-SC) versus ObsessiveCompulsive Inventory) and methods (current versus lifetime symptoms, dichotomous versus ordinal versus interval scoring, a priori categories versus item-level analysis, exploratory versus confirmatory factor analysis, factor versus cluster analysis). In a recent study, Hasler et al (20) demonstrated that the use of factor and cluster analysis in the same sample of patients yielded identical results. An important limitation, however, is that most studies employed the YBOCS-SC which was not designed to be used as a quantitative rating scale. Some of the symptom dimensions have been consistently replicated across studies (e.g. contamination/washing, symmetry/ordering, hoarding) but the aggressive/checking and sexual/religious dimensions need further study, as it is unclear whether they form a unique factor or can be broken down into

multiple separate dimensions. Similarly, it is unclear how to regard somatic obsessions, since they appeared on different dimensions in different studies. Thus, although this factor structure is still provisional and limited by the available instruments of measure, researchers have begun to examine the biological, behavioral and cognitive correlates of each of these symptom dimensions and, more importantly, to develop specific treatments for each particular problem.

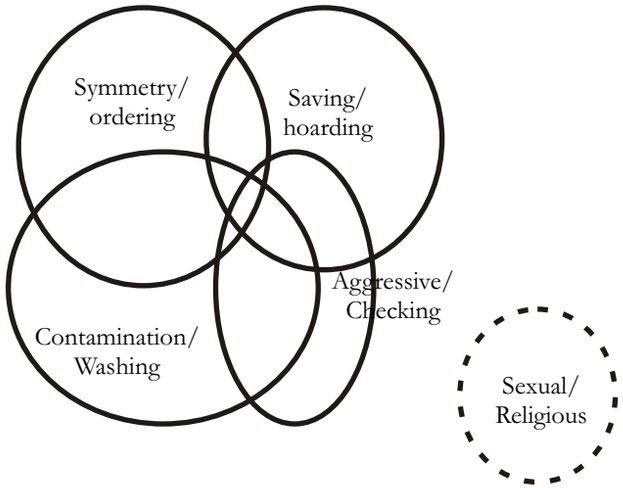

Figure 1. Schematic representation of the major symptom dimensions of OCD. Most studies consistently identified four symptom dimensions (continuous lines), while some others identified a fifth dimension consisting of sexual and religious obsessions (dashed line) but more research is needed to determine its validity. Note the overlap between these dimensions as mono-symptomatic patients are very rare.
Adapted from Mataix-Cols (17)

Temporal Stability of OCD Symptom Dimensions

Preliminary data support the temporal stability of the OC symptom

dimensions, at least in adult patients. Over a period of two to seven years, Rettew et al (32) assessed the longitudinal course of OC symptoms in 76 children and adolescents with OCD using the categories of the Y-BOCS-SC. They found that none of the patients maintained the same constellation of symptoms from baseline to follow-up. Nevertheless, these authors acknowledged that these changes could have occurred within, rather than, between symptom dimensions. This hypothesis was however not tested.

Two other studies, with large samples, have found that adult patients maintain their symptoms across time intervals as long as six years and the most robust predictor of having a particular symptom was having exhibited the particular symptom previously (33, 34). For symptoms that changed across time, changes typically occurred within, rather than between, previously identified symptom dimensions. This suggests that the symptoms of adult OCD patients are more stable than it is often assumed. A small study on children and adolescents also suggests that OCD symptom dimensions may be temporally stable in pediatric patients although this will require replication in larger samples (29). Finally, a recent two-year prospective study has found that the content of OC symptoms is also temporally stable in nonclinical samples (35). Longer longitudinal studies following patients from childhood to adulthood are needed to gain a more complete understanding of the natural history of OC symptoms.

The Relationship between OCD Symptom Dimensions and Comorbidity

Baer (36) reported that patients with high scores on his symmetry/hoarding factor were more likely to have a comorbid diagnosis of chronic tics and OC personality disorder (OCPD). Similarly, Leckman et al (37) found that patients

with high scores on the obsessions/checking and symmetry/ordering factors were more likely to present with tics. Mataix-Cols et al (38) found that male but not female OCD patients with chronic tics scored higher than patients without tics on the symmetry/ordering dimension. More recently, Hasler et al (20) found that the obsessions/checking dimension was broadly associated with comorbid anxiety disorders and depression, while the symmetry/ordering dimension was associated with bipolar disorders and panic disorder/agoraphobia. In the initial characterization of the DY-BOCS scale, depression and anxiety symptoms were also found to correlate with the severity of the aggressive obsessions and related compulsions (39).

There also appears to be a clear overlap with eating disorders. For example, Halmi et al (40) reported that approximately 70% of patients with anorexia nervosa (AN) had lifetime OC symptoms, especially symmetry and somatic obsessions and ordering and hoarding compulsions. And in another recent study, Halmi et al (41) emphasized the importance of 'perfectionism' as well as OCD and OCPD. In contrast, Hasler et al (20) reported an association between eating disorders and the contamination/cleaning dimension.

Mataix-Cols et al (42) examined the presence of all DSM-III-R Axis II diagnoses and their relation to OC symptom dimensions in a sample of 75 OCD patients. They found that hoarding symptoms were strongly related to the presence and number of all personality disorders, especially from the anxious-fearful cluster. Similarly, Frost et al (43) found that hoarding was associated with higher levels of comorbidity (i.e. anxiety, depression, personality disorders), as well as work and social disability, compared to nonhoarding OCD and other anxiety disorders. In another study (44), the

presence of hoarding was associated with increased prevalence of comorbid social phobia, personality disorders and pathological grooming conditions (skin picking, nail biting, and trichotillomania).

Taken together, these preliminary studies suggest that the presence of certain symptom dimensions may be associated with specific patterns of comorbidity. If confirmed in larger patient samples, these findings will have management implications as different treatment approaches may be indicated in each case.

Initial Validation from Family Genetic Studies

Family and twin studies suggest that genetic factors play a role in the expression of OCD. Recent advances in molecular genetics have greatly increased the capacity to localize disease genes on the human genome. These methods are now being applied to complex disorders, including OCD. Although earlier studies have indicated that the vertical transmission of OCD in families is consistent with the effects of a single major autosomal gene (45, 46), it is virtually certain that there are a number of vulnerability genes involved. One of the major difficulties in the application of these approaches is the likely etiologic heterogeneity of OCD and related phenotypes. Heterogeneity reduces the power of gene-localization methods, such as linkage analysis (47-49). Etiologic heterogeneity may be reflected in phenotypic variability, thus it would be highly desirable to dissect the syndrome, at the level of the phenotype, into valid quantitative heritable components.

Alsobrook et al (50) were the first to use OC symptom dimensions in a

genetic study. They found that the relatives of OCD probands, who had high scores on the obsessions/checking and symmetry/ordering factors, were at greater risk for OCD than were relatives of probands who had low scores on those factors. These findings have been recently replicated in a second independent family study (51).

The data used in genetics affected sibling pair study done by Leckman et al (52) was collected by the Tourette Syndrome Association International Consortium. Leckman et al (52) selected all available affected Tourette Syndrome (TS) pairs and their parents for which these OC symptom dimensions (factor scores) could be generated using the four factor algorithm first presented by Leckman et al (37). Over 50% of the siblings with TS were found to have comorbid OCD and more than 30% of mothers and 10% of fathers also had a diagnosis of OCD. The scores for both Factor I (obsessions/checking) and Factor II (symmetry/ordering) were significantly correlated in sibling pairs concordant for TS. In addition, the mother-child correlations (but not father-child correlations) were also significant for these two factors. Based on the results of the complex segregation analyses, significant evidence for genetic transmission was obtained for all factors.

A genome scan of the hoarding dimension was completed using the same TSAICG data set (53). The analyses were conducted for hoarding as both a dichotomous trait and a quantitative trait. Not all sib pairs in the sample were concordant for hoarding. Standard linkage analyses were performed using Genehunter and Haseman-Elston methods. Significant allele sharing was observed for both the dichotomous and the quantitative hoarding phenotypes for markers at 4q34, 5q35.2 and 17q25. The 4q site is in proximity to D4S1625, which was identified by the TSAICG as a region, linked to the TS phenotype. A

recursive-partitioning analytic technique also examined multiple markers simultaneously. Results suggest joint effects of specific loci on 5q and 4q. Another large linkage study in 219 families with multiple affected individuals found an association between the hoarding phenotype and a region in chromosome 14 (54). The inconsistencies between the Zhang et al (53) and Samuels et al (54) studies are most certainly due to marked differences in the family selection criteria (in the former study all probands had TS, whereas the latter excluded probands with TS). It is important to note that both studies were probably underpowered to find genes that are likely to have a small effect.

A recent study involving 418 sibling pairs with OCD (55) found that after controlling for sex, age and age of onset, robust sib-sib intraclass correlations were found for Factor IV (hoarding; $p = .001$) and Factor I (obsessions/checking; $p = .002$). Smaller, but still significant, sib-sib intraclass correlations were found for Factor III (contamination/cleaning; $p = .02$) and Factor II (symmetry/ordering; $p = .04$). Limiting the sample to female subjects more than doubled the sib-sib intraclass correlations for Factor II ($p = .003$).

Two studies (21, 56) have genotyped OCD patients for the functional polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) and both found that the frequencies of the S allele and the SS genotype were associated with the symmetry/order dimension. This is promising given that 5-HTTLPR remains a major candidate gene for OCD (57). This observation may also be consistent with the findings of Sutcliffe et al (58) who reported that within a large group of individuals with autism with rigid compulsive behaviors including ordering, symmetry and arranging - were more likely to have coding substitutions at highly conserved positions

and 15 other variants in 5' noncoding and other intronic regions within the 5-HTTLPR locus.

To summarize, the use of quantitative traits that are familial may provide a powerful approach to detect the genetic susceptibility loci that contribute to OCD presentations. So far, this approach has provided especially promising leads with regard to the hoarding OC phenotype, although the majority of these studies are probably underpowered. Twin studies of OCD symptom dimensions are now needed.

Initial Validation from Neuroimaging Studies

Functional neuroimaging studies have increased our understanding of the neural correlates of OCD symptoms, although not necessarily their causes. Neuroimaging studies so far strongly link OCD (as a whole) with dysfunction of the orbitofrontal cortex, with less consistent involvement of the basal ganglia, anterior cingulate gyrus, lateral frontal and temporal cortices, thalamus, amygdala and insula (59). We would predict that if a dimensional approach is useful, then a significant portion of the individual variation seen in these studies might be accounted for by the unique mix of symptom dimensions seen in any given patient. Initial studies generally support this conclusion.

In the first such study, using PET, Rauch (60) found that checking symptoms correlated with increased, and symmetry/ordering with reduced, regional cerebral blood flow (rCBF) in the striatum, while washing symptoms correlated with increased rCBF in bilateral anterior cingulate and left orbitofrontal cortex. Phillips (61) compared OCD patients with mainly

washing (n=7) or checking (n=7) symptoms, while viewing pictures of either normally disgusting scenes or washer-relevant pictures using fMRI. When viewing washing-related pictures, only washers demonstrated activations in regions implicated in emotion and disgust perception (i.e. visual regions and insular cortex), whereas checkers demonstrated activations in frontal-striatal regions and the thalamus.

In a similar study, eight OCD patients with predominantly washing symptoms demonstrated greater activation than controls in the right insula, ventrolateral prefrontal cortex and parahippocampal gyrus when viewing disgust-inducing pictures (62). Another study found increased amygdala activation in a group of 11 washers during the presentation of contamination-related pictures (63). Saxena et al (64) found that 12 patients with predominantly hoarding symptoms showed reduced glucose metabolism in the posterior cingulate gyrus (vs. controls) and the dorsal anterior cingulate cortex (vs. non-hoarding OCD) and that severity of hoarding in the whole patient group (n=45) correlated negatively with metabolism in the latter region. One recent fMRI study used a symptom provocation paradigm to examine, within the same patients, the neural correlates of washing, checking and hoarding symptom dimensions of OCD (65). Each of these dimensions was mediated by distinct but partially overlapping neural systems. While both patients and controls activated similar brain regions in response to symptom provocation, patients showed greater activations in bilateral ventromedial prefrontal regions (washing experiment), putamen/globus pallidus, thalamus and dorsal cortical areas (checking experiment), left precentral gyrus and right orbitofrontal cortex (hoarding experiment). These results were further supported by correlation analyses within the patient group, which revealed

highly specific positive associations between subjective anxiety, questionnaire scores and neural response in each experiment. Another recent study[66] demonstrated that 8 patients with predominant washing symptoms showed increased neural responses to disgusting (but not fearful) faces, compared to non-washing OCD patients (n=8) and healthy controls (n=19). Specifically, washers showed greater activation in the left ventrolateral prefrontal cortex (BA47) compared with the other two groups. Finally, a recent study by Rauch et al (67) tested for associations between OCD symptom factors and regional brain activation during an implicit learning task. They found that activation within right caudate was inversely correlated with symmetry/arranging and contamination/washing factors; left orbitofrontal activation was directly correlated with the sexual/religious/aggressive/counting factor.

Structural neuroimaging OCD studies have been remarkably inconsistent. Only one recent study examined the correlations between symptom scores and gray matter volumes. Pujol et al (68) found that patients with high scores on the aggressive/checking dimension had reduced gray matter volume in the right amygdala. The significance of this finding is unclear, especially since the convergent validity of the aggressive/checking factor of the YBOCS-SC is poor (69).

Taken together, these studies raise the question of whether the lack of perfect replicability of the findings in previous imaging studies of OCD could be accounted for by phenotypic variations among their subjects. If these preliminary findings are confirmed, and a consistent pattern of results can be documented by symptom factor, this would suggest that discrete neural systems may mediate the expression of different symptom dimensions.

Prediction of Treatment Response: Pharmacotherapy and other Somatic Treatments

While controlled trials with serotonin reuptake inhibitors (SRIs) have demonstrated a selective efficacy in OCD, up to 40-60% of patients do not have a satisfactory outcome. These differences in treatment outcome emphasize the heterogeneity of OCD and the need for identifying predictors of treatment response. While definitive studies have not been undertaken, recent studies have suggested that a symptom-based dimensional approach may prove to be valuable for identifying significant predictors of treatment outcome. For instance, several studies have shown that patients with high scores on the hoarding dimension respond more poorly to SRIs (27, 38, 70-73). In another study, high scores on the sexual/religious obsessions factor identified by Mataix-Cols et al (38) were associated with poorer long-term outcome with SRIs and behavior therapy in 66 adult outpatients who were followed up from one to five years (74). Two other groups have recently reported that the presence of sexual obsessions was a predictor of non-response to SRIs (75, 76). Shetti et al (75) also found contamination/washing symptoms were associated with non-response to SRIs. Another study (72) reported that patients with somatic obsessions had poorer insight and responded less well to SRIs.

Other somatic treatments may also help patients with specific symptoms. For instance, one study found that patients with symmetry and unusual somatic obsessions may respond well to monoamine-oxidase inhibitors (77). In another study, the presence of symmetry/ordering and hoarding predicted better response in refractory cases treated with cingulotomy (78). Clearly, this evidence is weak but underlines the need for careful measurement of specific symptom dimensions in all clinical trials of OCD.

Compliance and Response to Behavioral Interventions

The efficacy of Behavior Therapy (BT) for OCD has been demonstrated in numerous controlled and meta-analytic studies. However, a significant number of patients still remain unimproved or simply refuse or drop out from this treatment. Some studies have suggested that checking rituals may respond less well to BT (6, 79) but others found no differences in outcome between washers and checkers (80). Foa and Goldstein (80) however, reported that washers and checkers responded at different rates to behavioral treatments, with checkers being slower to respond. It is often assumed that patients with 'pure' obsessions and mental rituals respond less well to classic behavioral interventions, although data supporting these assumptions is sparse. In a meta-analysis, patients with primary obsessive thoughts without rituals tended to improve less with BT than those who had overt, motor rituals (81). In the Alonso et al (74) study, the presence of sexual and/or religious obsessions predicted poorer long-term outcome but, because most patients had both SRIs and BT, it was not clear from this study whether these symptoms predicted poorer outcome with SRIs, BT or both.

Patients with hoarding symptoms have been described as having poor compliance with and response to BT (82-84). For example, using a dimensional approach, Mataix-Cols et al (82) examined 153 OCD outpatients who took part in a randomized controlled trial of BT. Results showed that high scorers on the hoarding dimension were more likely to drop out prematurely from the trial and also tended to improve less than non-hoarding OCD patients. In addition, high scorers on the sexual/religious dimension responded less well to BT. Interestingly, patients with mental rituals did as well as other OCD patients in this study. Therefore, it seems that BT is mostly

indicated for patients with contamination/washing, aggressive/checking, and symmetry/ordering symptoms. Besides, previous anecdotal accounts of unsuccessful BT in patients with hoarding symptoms may be due in part to their propensity to drop out earlier from treatment. This work has led to the development of symptom-specific CBT protocols, in particular for hoarding symptoms, which are currently being tested in open (85) and controlled trials.

A Developmental Perspective

Children engage in a significant amount of ritualistic, repetitive, and compulsive-like activity that is part of their normal behavioral repertoire. Clinically, this phenomenon reaches a peak at about 24 months of age (86). Using the Childhood Routines Inventory (CRI) - a parent-report questionnaire - to assess compulsive-like behavior in young children, Evans et al (87) collected data from 1,492 parents with children between the ages of 8 and 72 months of age.

The CRI was found to have a strong internal consistency and a two-factor structure. The first factor accounted for 33% of the variance and included items such as 'lines up objects in straight lines or symmetrical patterns,' 'arranges objects or performs certain behaviors until they seem *just right*,' and 'prefers to have things done in a particular order'. Evans et al (87) found the early emergence of specific behaviors that resemble the symptom dimensions observed in OCD patients. For example, parents reported that their children 'arranged objects or performed certain behaviors until they seemed *just-right* on average, beginning at age 22 to 25 months. Similarly, behaviors resembling those associated with the contamination/washing dimension identified with such questions as, 'seemed very concerned with dirt or cleanliness' were found

to have their mean age of onset from 22 to 24 months. Finally, parents reported that their children on average began to 'collect or store objects' (resembling the hoarding dimension) from 25 to 27 months of age.

Although direct evidence linking the emergence of these behaviors to the later development of OCD is lacking, investigators have found that aspects of these ritualistic and compulsive-like behaviors are correlated with children's fears and phobias (88, 89). Further exploration of the factors that underlie the emergence and resolution of these behaviors in normally developing children may provide valuable insights into the neurobiological substrates and evolutionary origins of these behaviors.

An Evolutionary Perspective

The ultimate causes for many neuropsychiatric disorders including OCD are likely built into the genetic and neurobiological mechanisms that underlie highly conserved behavioral and cognitive repertoires (90-93). In the case of OCD and its composite dimensions, such an evolutionary perspective seems particularly apt. Indeed we hypothesize that each of these OC dimensions evolved to deal with specific threats (Table 2). It is plausible that if our forbears had not been acutely attuned to potential external threats posed by other humans, by predators, by the external manifestations of microbial disease, or periods of privation due to drought, natural disasters, or internecine conflict, our species would not have survived.

Specifically, it is probable that during our evolutionary history there were times of great privation such that hoarding was adaptive and likely to enhance the likelihood of survival and reproductive success. A similar argument can be

Table 2: Threat domains, conserved behaviors and developmental epochs associated with heightened sensitivity and obsessive-compulsive like behaviors.
Adapted from Leckman et al (18).

Threat domain	Focus of concern	Mental state	Behavioral response	Developmental epochs
Harm from aggressive behavior from conspecifics	Well-being of self and close family members	Intrusive images or thoughts that contain feared outcomes of separation or loss; Among older children and adults-a heightened sense of responsibility	Physical proximity; Checking to ensure the safety of close family members; Avoidance of danger	Early childhood - formation of attachment to caregivers; Early family life - pregnancy, delivery and care of young children; Threats to family members due to injury or other external threats
Physical security	Immediate home environment	Heightened attention to the placement of specific objects in the environment	Checking to ensure that things look 'just right' and are in their expected places; arranging/ordering objects	Early childhood - Initial period of exploration of the home environment by infants and toddlers; Early family life - pregnancy, delivery and early childhood; Threats to family members due to injury or other external threats
Environmental cleanliness	Personal hygiene; Hygiene of family members; Cleanliness of the home	Preoccupation with intrusive images or thoughts that contain feared outcomes of being dirty or causing others to be ill	Washing/cleaning; Avoidance of shared or disgusting items; Checking to ensure cleanliness	Early childhood - Initial period of selection of items of food and drink by toddlers; Early family life - pregnancy, delivery and care of young children; Threats to family members due to injury or other external threats
Privation	Essential resources	Preoccupation with loss and feared outcomes of privation	Collecting items; Checking to ensure the sufficient supplies are available	Latency - Initial period of collecting; Early family life - pregnancy, delivery and care of young children

made for each of the other dimensions, e.g., that compulsive checking to see that items in the home environment were *just right* and not out of place or ensuring that food and key aspects of the home environment were free of contamination would have served families well at some points in what Darwin called 'the struggle for life'.

The possible evolutionary origins of obsessions and compulsions related to fears about harm befalling a close family member are of particular interest as they may reveal something of the normal states of heightened preoccupation that are associated with formation of intimate interpersonal relationships. For example, for expectant parents, the immediate perinatal period involves an altered mental state characterized by excitement, and heightened sensitivity to environmental and emotive cues. The infant becomes an increasingly exclusive focus of thought and action towards the end of pregnancy and the early postpartum period. Cues from the infant before and after birth as well as the infant's proximity, physical appearance, and temperament provide a major stimulus for these preoccupations and associated behaviors. Guided by this perspective, Leckman et al (93) recently completed a prospective longitudinal study of 80 expectant parents using a modified version of the Y-BOCS. Consistent with their a priori hypothesis the content of the parents' preoccupations involved anxious intrusive thoughts and harm avoidant behaviors that closely resemble some obsessions seen in OCD patients with aggressive symptoms, namely, worries about aggressive behavior, unintentional or intentional, that would lead to the baby being harmed were commonplace. Consistently, such intrusive thoughts were relieved by the performance of compulsive checking behaviors that the parents may regard as excessive or unnecessary.

Viewed from an evolutionary perspective, it seems nearly self-evident that the behavioral repertoires associated with early parenting skills would be subject to intense selective pressure. For one's genes to self-replicate, sexual intimacy must occur and the progeny of such unions must survive. Pregnancy and the early years of an infant's life are fraught with mortal dangers. Indeed, it has only been during the past century that infant mortality rates have fallen from over 100/1,000 live births in 1900 to about 10/1,000 at present. Little wonder then that a specific state of heightened sensitivity on the part of new parents would be evolutionarily conserved.

Consistent with the emerging data from brain imaging studies, this evolutionary perspective suggests that each of the OC symptom dimensions is based on overlapping brain-based alarm systems that have the potential to become dysregulated due to genetic vulnerability, adverse environmental change during the course of development (maladaptive learning leading to brain changes), or brain injury. Viewed in this light, the diverse behaviors and mental states encountered in OCD are not in themselves pathological. It is only by the distress they cause, their persistence and their tendency to occupy time to the exclusion of more normal activities that they become pathological.

Expert Opinion

We have recently conducted a survey among World OCD experts asking them about several contentious issues regarding the future classification of OCD and related disorders in the DSM-V (94). Regarding the potential sub-typing of OCD, a majority of experts agreed with the usefulness of a tic-related (81% agreed) and early age of onset subtypes, although they disagreed

regarding the definition of early onset OCD: before age 10 (66% agreed) or before age 18 (49% agreed). A majority of experts (89%) agreed that OCD is heterogeneous and that it will be important to document the presence of its major symptom dimensions as specifiers in the DSM-V.

Conclusions

The complex clinical presentation of OCD can be summarized using a few consistent and temporally stable symptom dimensions. These can be understood as a spectrum of potentially overlapping syndromes that are likely to be continuous with 'normal worries' and extend beyond the traditional nosological boundaries of OCD (16-18). Although the dimensional structure of OC symptoms is still imperfect, this quantitative multidimensional approach has the potential to advance our understanding of the broad entity that we call OCD. Preliminary data suggest that these dimensional phenotypes may be useful in studies of the genetics, neurobiology and treatment outcome of OCD. A dimensional approach is not incompatible with other useful ways to subtype OCD, such as early age of onset and the presence of comorbid tics (95-98). It is clear that new clinical rating instruments such as the DY-BOCS (39) are needed to further explore the dimensional structure of OC symptoms and measure the severity of symptoms within each dimension. These new instruments should permit the development of better quantitative traits for research as well as more discriminating data for use in clinical trials. Finally, clinical researchers should aim to develop specific interventions for specific symptom dimensions as clearly 'one size does not fit all'.

Note

This review is based on earlier reviews by the authors: Mataix-Cols D, Rosario-Campos MC, Leckman JF. A multidimensional model of Obsessive-

Compulsive Disorder. Am J Psychiatry 2005;162: 228-238; Mataix-Cols D. Deconstructing obsessive-compulsive disorder: A multidimensional perspective. Curr Opin Psychiatry 2006;19: 84-89; Leckman JF, Rauch SL, Mataix-Cols D. Symptom dimensions in Obsessive-compulsive disorder: Implications for DSM-V. CNS Spectr 2007; 12: 376-400.

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Chapter 3

Neurobiology of Obsessive-Compulsive Disorder

Venkatasubramanian Ganesan

Introduction

Earlier approaches to understand Obsessive-Compulsive Disorder (OCD) emphasized on the importance of psychodynamic processes to explain obsessive-compulsive symptoms (1). For example, Freud argued that obsessive-compulsive character, obsessive-compulsive neurosis, and obsessive-compulsive psychosis lay on a spectrum and were all characterized by specific unconscious mechanisms like heightened anal drive. Failure of these defence mechanisms led to the genesis of obsessive-compulsive symptoms. Though such explanations helped in understanding the phenomenology of OCD, they lacked empirical support and more importantly they did not pave the way for effective treatments (2).

Subsequent approaches have banked on cognitive-behavioral mechanisms to explain OCD (3). According to the cognitive behavioural model, obsessions are construed as intrusive thoughts that heighten one's anxiety and compulsions are viewed as cognitions or conations that neutralize obsessions and reduce anxiety. This approach resulted in formulating effective interventions for OCD (4). While this model is useful as an explanatory approach towards the immediate or proximal basis for the genesis of OC symptoms, it does not advance our understanding beyond this. Besides, this

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approach does not account for various observations demonstrating biological abnormalities in OCD.

Further approaches have adopted biological means to explain OCD. The major tenets of biological models are based on:

i) psychopharmacology research showing serotonin-reuptake inhibitors being more effective than noradrenaline-reuptake inhibitors in alleviating OC symptoms
ii) neuroimaging research demonstrating brain abnormalities in OCD.

Recent advances in biological psychiatry research, especially those that utilize cutting-edge techniques, have rendered vital insights towards understanding OCD. Indeed, these advances have blurred the rigid boundaries between psychology and biology and have led to integrated neurobiological models that facilitate a comprehensive understanding about the genesis of OCD.

The concept of Endophenotype has returned to the fore to facilitate an understanding of neurobiological perspectives of various psychiatric disorders manifestations including OCD (5). Endophenotypes, measurable components unseen by the unaided eye along the pathway between disease and distal genotype, have thus emerged as an important concept in the study of complex neuropsychiatric diseases. An endophenotype may be neuropsychological, neuroanatomical, neurophysiological, or biochemical in nature. Along these aspects, this selective overview aims to examine the neurobiological basis of OCD by summarizing various studies.

At the outset, a focused summary of the OCD symptoms is presented with specific emphasis on its relationship to the neuropsychological deficits or a more proximal endophenotype. The subsequent section attempts to establish the link between the symptom expression and neuropsychological aberrations. The brain basis of these neuropsychological deficits in OCD is reviewed later. A further section aims at elucidating the micro-architectural abnormalities (i.e. neurotransmitter, neurochemical & other related abnormalities) that have been demonstrated to underlie these brain abnormalities. This would be followed by a brief summary of the current understanding of the genetic basis of the cascade of abnormalities. Finally, an integrated neurobiological model of OCD is proposed that incorporates various facets of neurobiological aberrations that have been demonstrated as outlined above.

OCD Symptoms: A Glimpse

OCD is a relatively common disorder with a lifetime prevalence ranging from 1.9% to 3.3% (6). Studies suggest that OCD is the fourth most frequent psychiatric condition following phobias, substance abuse and major depression. OCD is characterized by the presence of obsessions and compulsions. As per DSM-IV, obsessions are defined by the following characteristics:

(i) recurrent and persistent thoughts, impulses, or images that are experienced, at some point during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
(ii) thoughts, impulses, or images that are not simply excessive worries about real-life problems
(iii) attempts by the person to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action,

(iv) recognition that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from outside as in thought insertion).

Compulsions on the other hand are defined by,

(i) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly

(ii) behaviors or mental acts that are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are either not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.

Studies using factor analysis statistics have reported classification of OCD symptoms into three to five major distinct symptom clusters including: (a) aggressive and somatic obsessions with checking compulsions; (b) symmetry and exactness preoccupations with counting, arranging and ordering rituals; (c) fears of contamination and illness with washing and cleaning compulsions; (d) hoarding concerns with collecting compulsions; and (6) sexual and religious obsessions (7-10).

It has been suggested that the unifying phenomenological theme that underlies the obsessions is the impression that 'something is wrong' (11). According to this view, obsessions can be conceptualized as an enduring perception of an error in specific instances that will invariably result in mounting anxiety. Compulsions are behavioral (or cognitive) responses that

serve to reduce this anxiety. Though the resulting anxiety-free state is rewarding, because of its transient nature, is followed by an intrusive recurrence of 'obsessional state' with repetition of compulsive behavior (or cognition). Such a conceptualization, though simplistic, suggests deficits in various crucial cognitive functions that might potentially underlie the genesis of OC symptoms such as:

(i) attention impairments (caused by the intrusiveness of OC symptoms),

(ii) memory impairment (OCD patients might forget to do certain activities, for example locking the door)

(iii) error monitoring (caused by the enduring 'something is wrong' feeling),

(iv) emotion processing, motivation-reward systems and response inhibition (caused by the tendency of these patients to persist with compulsions because of the short-term rewards).

Neuropsychological Deficits in OCD

Neuropsychological studies have systematically examined the OCD patients for deficits along the suggested predictions as mentioned above. This section attempts to provide a brief and selective overview of various neuropsychological deficits that have been described in OCD.

Attention Deficits in OCD

While studies have indicated lack of pure attention deficits in OCD (12, 13), potential attention bias towards stimuli relevant to OC symptoms (for example contamination related words) has been reported (14). Interestingly, a significant negative correlation between the age at onset of OCD symptoms

and the reaction time for color-word interference (i.e. the younger the onset of the OCD the more severe are the attention deficits) has been observed (15). A neurodevelopmental subtype of OCD has been proposed that is characterized by childhood onset, predominantly male sex and poorer response rate to treatment, neuromotor abnormalities and increased comorbidity with ADHD and Tourette's disorder. The rate of comorbid mood disorder was also significantly lower in children than in adults (16). Differences on neuropsychological tests have also been reported between the subgroups in different domains (17, 18). These findings suggest that attention processes might be differentially impaired in sub-types of OCD with relevance to the age-at-onset. This requires systematic assessment in future studies.

Memory Deficits in OCD

Careful assessment of the clinical profile of OCD patients would suggest 'memory deficits' as a potential heuristic with a query on the authenticity of these deficits. The query arises since these can also be secondary to the patients having diminished confidence in their memory (in the absence of actual memory deficits). Studies assessing the first component of this heuristic (i.e. memory deficits in OCD) have yielded contradictory results with some reporting episodic memory deficits (19, 20) as well as verbal memory deficits (21) while other reporting no deficits (22). Interestingly, OCD patients were even found to have rather better (than poor) memory for actions (23). A meta-analysis by Woods et al (24) concluded that OCD patients (especially the checkers) demonstrated a memory deficit in recall but not in recognition of verbal materials. Impairments in OCD demonstrated by tasks like Rey Complex Figure Test suggest that deficits exist in recall performance on these tasks in OCD. However, it has been argued that this impairment is due to

failures in the employment of appropriate organizational strategies (25).

Researchers have speculated some of the inconsistent findings with relevance to memory deficits in OCD could possibly due to the second component of the above mentioned heuristic (i.e. patients having diminished confidence in their memory). This led to examination of 'metamemory' in OCD. Metamemory refers to our knowledge of the nature, content, and processes of memory-related phenomena (26). Indeed, studies have shown that OC patients with checking compulsions have diminished confidence in their memories (22). Further analysis of metamemory deficits in OCD show that this might be specific to recently experienced materials that semantic memory (27).

Another influencing factor on memory as well as metamemory deficits in OCD is the 'perceived personal responsibility.' It has been hypothesized that a lowered threshold for perceived personal responsibility results in establishment of OCD (i.e. in situations which might not bother most people, OCD patients overestimate their share of responsibility and hence feel the need to prevent some catastrophe by means of certain rituals and precautions). In fact, studies have supported this hypothesized association between perceived responsibility and obsessionality (28, 29). A recent study has shown that 'perceived responsibility' can influence the confidence in memory in OCD (30) where patients demonstrated low memory confidence in situations where perceived responsibility was high. To summarize, memory as well as metamemory deficits especially in the context of heightened 'perceived personal responsibility' might lead to enhanced self-scrutiny with intense action monitoring (31) with associated anomalous error monitoring functions in OCD.

Emotion Processing, Motivation & Reward System and Response Inhibition Deficits in OCD

Broad evidence has been provided that subjects with OCD share a processing bias for emotionally arousing material (32). It has been speculated that some pathological behaviors in OCD patients are strictly connected to maladaptive perception of reward (33). Phillips et al (34) have shown that, while in a non-pathological condition the normal desire to wash the hands after touching a dirty object disappears after the hands are washed, compulsive washers never perceive 'satiety' and continue to feel forced to wash themselves. At the same time, acting on compulsions (negative reinforcement), they obtain a temporary relief of anxiety (reward) but never feel 'full'. In relation to this, search for an immediate reward (relief of anxiety from compulsions), lack of behavioral flexibility (continuous repetition of the same behavior), and blindness to negative future consequences the 'myopia for the future' (resulting in compromised life-quality) have all been described as characteristic traits of OCD patients (33).

These traits and the associated symptoms can result in complete disruption of planning and execution of real-life strategies with impairments in decision making. Decision making refers to the process of forming preferences, selecting and executing actions, and evaluating outcomes (35). OCD patients have been examined for impairments in decision making using various tests which are theoretically distinguished on the basis of how they operationalize the processes involved in decision making. Certain tasks are based on the concept of delay and others on the notion of risk. Delay-based tasks require subjects to choose between small, immediate rewards or larger, delayed rewards and the optimal choice is to choose delayed rewards. Otherwise, risk-

based tasks contain elements of uncertainty, and in order to succeed participants must adopt a preference for small but certain rewards over larger, uncertain rewards. These latter tasks are classified as probabilistic or risk-taking tasks (as reviewed in 33).

Using gambling task, a study by Cavedini et al (36) investigated decision-making function in OCD patients with panic disorder patients and healthy subjects as comparison groups. The gambling task was originally described by Damasio and his coworkers to assess the decision making abilities in patients with ventromedial frontal lesions. Cavedini et al (33), in their review, summarized the gambling task. This task requires 100 card selections from four decks of cards identical in appearance; subjects are asked to maximize their profit starting from a $2000 loan of play money. To attain this goal they must find the most advantageous decks and persistently pick up cards from those decks. After turning over some cards, subjects are both given money and sometimes asked to pay a penalty according to a pre-programmed schedule of reward and punishment. Gains and losses are different for each card selected from the four decks. Decks A and B are 'disadvantageous,' since the penalty amounts are higher despite paying $100. Hence, they cost more in the long run. Decks C and D are 'advantageous' since the penalty amounts are lower. Hence though they pay only $50, the resulting overall gain increases in the long run. To summarize, decks A and B are equivalent in terms of overall net loss over the trials, as are decks C and D; the difference is that in decks A and C the penalty is more frequent, but of smaller magnitude, while in decks B and D the penalty is less frequent but of larger magnitude.

In the gambling task, there were differences in performance between OCD

and panic patients (36). The OCD subjects showed a significant preference for the disadvantageous decks, while panic and control subjects made significantly more selections from the advantageous decks, avoiding the bad decks. Analysis of the 100 card selections demonstrated that control subjects and patients with panic disorder started from random choices and gradually shifted their preferences toward the 'good' decks during the test. By contrast, OCD patients failed to operate this shift in card selection: they rapidly shifted their preferences toward the 'bad' decks, encouraged only by the prospect of immediate gain. Analysis of strategies adopted by OCD patients from the beginning to the end of the test suggested that during the 100 selections, all subjects understood the differences that characterize the four decks. However, while control subjects and panic patients increased the number of advantageous choices, OCD patients deliberately increased the number of disadvantageous selections. OCD patients appeared to be encouraged greatly by the prospect of immediate reward, being less sensitive to the future consequence of their choices. More importantly (although not unequivocally), this impairment seems to be a trait rather than a state in OCD patients (33).

Such decision-making impairments also suggest executive dysfunction in OCD. Indeed, a recent comprehensive review suggests that executive dysfunction could be a major neuropsychological deficit in OCD. Executive performances in attentional set-shifting, verbal fluency, planning and decision making, while often performed at a similar overall level of achievement to controls, are characterized by increased response latencies, perseveration of previous (inappropriate) responses, and difficulties in effectively utilizing feedback to adapt to changing conditions and environments. Whether these

deficits are secondary to generalized slowing of cognitive speed, increased checking behaviour in an attempt to avoid making mistakes, an inability to spontaneously generate alternative solutions and organizational strategies, or simply indecision when evaluating and choosing between alternatives, is yet to be determined (37).

Neuropsychological Deficits in OCD: Summary

To summarize, neuropsychological studies have established cognitive deficits in OCD (for comprehensive reviews see 25, 38). The potential confounding effects of comorbid psychiatric disorders as well as psychotropic medications need further elucidation. However,some of the consistent deficits that emerge include memory & executive function deficits in addition to emotion & reward system deficits. As reviewed above, one can speculate that the memory deficits could potentially be due to defective organization strategies (a component of executive function) as well as influencing emotional states (for example, perceived personal responsibility). This reduces the cognitive deficits to be grouped between executive versus emotional deficits. The former is coordinated primarily by the dorsolateral prefrontal cortex and the latter by the ventral prefrontal cortex. Both these brain regions (and the functions sub-served by them as well) are influenced by interactions with the anterior cingulate cortex. Such a view, though simplistic, is useful as a preliminary heuristic to understand the complex neural circuitry abnormalities suggested by these neuropsychological deficits. The subsequent section aims at reviewing the brain abnormalities in OCD.

Brain Abnormalities in OCD

The neuropsychological deficits in OCD suggest abnormalities in specific

brain circuits namely the fronto-striato-pallido-thalamo-frontal loop in these patients. The frontal-subcortical circuitry provides a unifying framework for understanding processes that control cognition, decision-making, the planning of complex behavioral strategies, and neuropsychiatric symptoms (39). This consists of a series of parallel segregated frontal-subcortical circuits now known to link specific regions of the frontal cortex to the striatum, the globus pallidus and substantia nigra, and the thalamus, constituting an important effector mechanism that allows the organism to interact adaptively with its environment.

The major frontal-subcortical circuits include three behaviorally relevant circuits with origins in the prefrontal cortex: a dorsolateral prefrontal circuit, which mediates 'executive' functions (i.e., the organization of information to facilitate a response); an anterior cingulate circuit, which is involved in motivational mechanisms and an orbitofrontal circuit, which has lateral and medial divisions. In addition, two other circuits sub serving motor functions - namely the motor circuit (originating in the supplementary motor area) and the oculomotor circuit (originating in the frontal eye field) that constitute the five frontal-subcortical circuits.

The dorsolateral prefrontal circuit originates in Brodmann's areas 9 and 10 on the lateral surface of the anterior frontal lobe. Neurons in these regions project to the dorsolateral head of the caudate nucleus. Fibres from this region of the caudate project to the lateral aspect of the mediodorsal globus pallidus interna and rostrolateral substantia nigra (pars reticulata) via the direct pathway. The indirect pathway sends fibres to the dorsal globus pallidus externa, which in turn projects to the lateral subthalamic nucleus; fibres from

the lateral subthalamic nucleus then terminate in the globus pallidus interna substantia nigra pars reticulata complex. Output from the basal ganglia projects to parvocellular portions of the ventral anterior and mediodorsal thalamus, respectively. The mediodorsal thalamus closes the circuit by projecting back to the circuit's origin in areas 9 and 10 of the dorsolateral frontal lobe.

The lateral division of the orbitofrontal circuit originates in the lateral orbital gyrus of Brodmann's area 11 and the medial inferior frontal gyrus of the areas 10 and 47 in humans. These areas send projections to the ventromedial caudate, which projects in turn to the most medial portion of the mediodorsal globus pallidus interna and to the rostromedial substantia nigra (pars reticulata). The ventromedial caudate also sends an indirect loop through the dorsal globus pallidus externa to the lateral subthalamic nucleus, which then projects to the globus pallidus interna and substantia nigra (pars reticulata). Neurons are sent from the globus pallidus and substantia nigra to the medial section of the magnocellular division of the ventral anterior thalamus, as well as an inferomedial sector of the magnocellular division of the mediodorsal thalamus. This division of the circuit then closes with projections from this thalamic region to the lateral orbitofrontal cortex. A medial division of the orbitofrontal circuit has also been identified, originating in the inferomedial prefrontal cortex, specifically the gyrus rectus and the medial orbital gyrus of Brodmann's area 11 in humans. From this area, the medial division has sequential projections to medial aspects of the accumbens, to medial ventral portions of the pallidum, and thence, via the medial magnocellular division of the mediodorsal thalamic nucleus, back to the medial orbitofrontal cortex. The medial orbitofrontal cortex has reciprocal

connections with the medial portion of the basal and the magnocellular division of the accessory basal amygdale. Cortical areas that have reciprocal connections with the medial orbitofrontal cortex influence visceral function when stimulated, probably through their shared amygdalar connections. Other regions reciprocally connected with the medial orbitofrontal cortex include the rostral insula, ventromedial temporal pole and brain regions related to the anterior cingulate circuit.

Neurons of the anterior cingulate serve as the origin of the anterior cingulate-subcortical circuit. From Brodmann's area 24, they provide input to the ventral striatum which includes the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle. This area is termed the limbic striatum. Projections from the ventral striatum innervate the rostromedial globus pallidus interna and ventral pallidum (the region of the globus pallidus inferior to the anterior commissure), as well as the rostrodorsal substantia nigra. There may also be a less well-defined indirect loop projecting from the ventral striatum to the rostral pole of the globus pallidus externa. The external pallidum in turn connects to the medial STN, which returns projections to the ventral pallidum. The ventral pallidum provides limited input to the magnocellular mediodorsal thalamus. The anterior cingulate circuit is closed with projections from the dorsal portion of the magnocellular mediodorsal thalamus to the anterior cingulate.

All the frontal-subcortical circuits have direct as well as indirect pathways. In the direct pathway, an excitatory glutamatergic signal projects to the striatum, sending an inhibitory gamma-aminobutyric acid (GABA) signal to the globus pallidus interna. This signal results in a decreased inhibition

(disinhibition) of the thalamus and thus an increased excitatory effect on the prefrontal cortex. In the indirect pathway, the striatum projects an inhibitory signal to the external part of the globus pallidus and the subthalamic nucleus, sending an excitatory signal to the globus pallidus interna. The net effect is an increased inhibition of the thalamus and decreased excitation of the prefrontal cortex. The direct pathway contributes to the initiation and continuation of behaviors whereas the indirect pathway plays a critical role in the behavioral inhibition and in switching between behaviors*. Fronto-striato-thalamo-frontal circuit abnormalities with an imbalance between these two pathways has been hypothesized to underlie the OCD (for review, see 2).

Neuroimaging studies have demonstrated findings in tune with this postulation. Neuroimaging studies have used various techniques to examine the brain basis for OCD which include

i) structural Magnetic Resonance Imaging (MRI) to assess the grey and white matter status,
ii) Magnetic Resonance Spectroscopy (MRS) to assess the neurochemical concentrations in these brain regions,
iii) Positron Emission Tomography as well as functional MRI to assess brain function abnormalities, and
iv) Diffusion Tensor Imaging to assess the white matter connectivity.

Structural MRI Studies

Volume reduction of the orbitofrontal cortex is one of the consistent findings that haves been shown in patients with OCD. Szeszko et al (40) reported bilateral OFC volume reduction in OCD; Choi et al (41) reported reduction of volume of left anterior OFC in OCD. Using an automated

*A mnemonic that might be of use is **D**irect **D**isinhibits **I**ndirect **I**nhibits

statistical parametric mapping approach Pujol et al (42) demonstrated volume deficit in medial OFC. On the contrary, two voxel-based morphometry studies have reported increased volume of OFC in OCD (specifically left anterior OFC (43) and increased left posterior OFC (44)).

The contradicting findings have been speculated to be secondary to the potential confounding issues of varying clinical profile of patients across different studies for example, the status of comorbid major depression or the predominant OC symptom profile of the patients. Interestingly, the presence of comorbid major depressive disorder can influence the OFC volumetric abnormalities. In a recent study by Cardoner et al (45), it was observed that OCD patients with comorbid major depressive disorder had larger reduction of OFC volume. It has been suggested that regional brain volumes in OCD might vary as a function of the severity of specific OCS dimensions (46), and this could increase the variability of results across different MRI investigations. Also, the orbitofrontal cortex presents heterogeneous functional subdivisions, each of which might play separate roles in the pathophysiology of different OCD features (47).

Volume reduction of OFC was shown to have significant positive correlation with Rey-Osterrieth Complex Figure Test Score suggesting that this deficit might be related to impaired organizational strategies in OCD (41). Kang et al (48) showed that OFC volume reduction is significantly correlated with the symptom severity in OCD. Interestingly, treatment refractory patients were shown to have significantly smaller bilateral OFC volumes than first contact patients. This further strengthens the role of OFC in the pathogenesis of OCD (49).

Studies have demonstrated volumetric deficits in another key region that is implicated in OCD namely, the cingulate cortex. In a recent study by Carmona et al (50), paediatric OCD patients showed significant reduction in cingulate volume in comparison to healthy controls. Cingulate abnormalities were also demonstrated in other studies (51, 52). These findings support volumetric deficits in error-monitoring regions in OCD.

Propelled by the hypothesized anomalous frontal-subcortical circuitry in OCD, studies have examined caudate nucleus volume in OCD. Studies have shown reduced (53), increased (54) as well as normal caudate volume in OCD (55). Intriguingly, women patients with OCD and Trichotillomania did not demonstrate caudate volume deficits (56) suggesting that that the varying sex composition of the caudate studies might have contributed to the conflicting findings. However, in this study, a significant correlation was observed between the caudate volume reduction and impaired performance on neuropsychological tests as well as higher neurological soft signs scores (56). A longitudinal study examining the patients before and after stereotactic subcaudate capsulotomy showed volume reduction of caudate nuclei, hippocampus as well as the anterior limb of the internal capsule suggesting that these structures might play a crucial role in OC symptoms genesis (57).

MRI volumetric deficits in other brain regions namely the thalamus (58), amygdala-hippocampal complex (59) and superior temporal cortex (60) have also been reported in OCD. It has been suggested that decreased OFC volume with increased thalamic volume might underlie treatment refractoriness in OCD (49). Some of the factors that might have contributed to contradicting findings in MRI studies include treatment status of the

patients, examination of sub-types and analysis methodology. However, one can derive a consensus finding regarding consistent demonstration of deficits involving OFC, cingulate cortex as well as striatal regions in OCD.

Functional Imaging Studies

Neuroimaging studies examining brain function in OCD patients have contributed crucial insights into the pathogenesis. These studies have utilized various techniques namely Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and functional MRI. ^{18}Fluorodeoxyglucose PET (FDG-PET) is a high resolution imaging technique that measures cerebral glucose consumption over a period of time (for example, 30 min) and has been shown to be a highly sensitive indicator of cerebral metabolic rate for glucose. Technetium-99m (^{99m}Tc)-hexamethylpropyleneamine-oxime SPECT (HMPAO-SPECT) is a measure of regional cerebral blood flow.

Studies utilizing FDG-PET report increased glucose metabolism in the orbitofrontal cortex (OFC), caudate, thalamus, prefrontal cortex, and anterior cingulate among patients with OCD as compared with healthy controls (61, 62). SPECT studies have alternatively found both increased and decreased blood flow to various brain regions including the OFC, caudate, various areas of the cortex, and thalamus in OCD patients as compared with normal controls (63, 64). A meta-analytic review of PET and SPECT studies concluded that hyperactivity of the orbitofrontal cortex (specifically the orbital gyrus) and the head of the caudate nucleus as the robust brain functional abnormalities that reliably differentiated OCD patients and healthy controls (65).

Functional MRI (fMRI) is a non-invasive imaging technique that is based

upon the differential magnetization properties of the hemoglobin. Hemoglobin is diamagnetic when oxygenated but paramagnetic when deoxygenated. The magnetic resonance (MR) signal of blood will therefore differ depending on the level of oxygenation of hemoglobin. These differential signals can be detected using an appropriate MR pulse sequence as Blood-Oxygen-Level-Dependent (BOLD) contrast. By collecting data in an MRI scanner with parameters sensitive to changes in magnetic susceptibility one can assess changes in BOLD contrast. These changes can be either positive or negative, depending upon the relative changes in both cerebral blood flow (CBF) and oxygen consumption. Increases in CBF that outstrip changes in oxygen consumption will lead to increased BOLD signal. Conversely decreases in CBF that outstrip changes in oxygen consumption will cause decreased BOLD signal intensity (as depicted in diagram below) (66).

Flow Chart Diagram Describing the Basics of Functional MRI

Regional brain activity

↓

Increase in oxygen utilization

↓

Disproportionate increase in local blood flow

↓

Net increase in local oxy-hemoglobin
(and decrease in local deoxy-hemoglobin concentration)

↓

Stronger MRI signal

Functional Magnetic Resonance Imaging Studies

Review of structural MRI studies has implicated brain volume abnormalities in frontal-subcortical circuit and limbic regions in OCD with the focal brain regions being orbito-frontal and anterior cingulate cortices, caudate, thalamus and amygdale. These brain regions are involved in crucial cognitive functions that are postulated to be abnormal in OCD namely the response inhibition, error monitoring and executive functioning. fMRI studies in OCD have attempted to clarify the precise nature of brain hemodynamic abnormalities in these regions with relevant task performance.

As discussed earlier, the unifying phenomenological theme that might underlie the obsessions is the impression that 'something is wrong' (as reviewed in 11). Since this can be associated with 'perceived personal responsibility', one would expect hyper-vigilant error monitoring systems in OCD. Anterior Cingulate Cortex (ACC) is considered to be one the primary regions associated with error monitoring (67, 68). Based on cytoarchitecture, function and connectivity, the ACC has been divided into dorsal (dACC) and rostral (rACC) sub-regions. The dACC extends caudally from the genu of the corpus callosum to the vertical plane of the anterior commissure and connects with the lateral prefrontal cortex and hippocampus to regulate effortful cognitive operations. This is also called as the 'cognitive division' cognitively demanding tasks that involve stimulusresponse selection in the face of competing streams of information, including Color Stroop and Stroop-like tasks, divided-attention tasks, verbal- and motor-response selection tasks and many working-memory tasks (67). The rACC lies anterior and ventral to the genu of the corpus callosum. The rACC, also called as the 'affective division' of the ACC, exhibits strong connectivity with limbic structures, such as the

amygdala, ventral striatum, and orbitofronal cortex (69). The rACC is activated by aversive stimuli (70) and mediates affective response to errors (71-73).

In an event-related fMRI study by Fitzgerald et al (74), OCD patients and healthy subjects were examined using the 'sflanker interference task' which is a simple cognitive task designed to elicit errors but not OCD symptoms. While both OCD patients and healthy subjects demonstrated dorsal ACC activation during error commission, the former demonstrated exhibited significantly greater error-related activation of the rostral ACC than comparison subjects. Moreover, activity in this region was positively correlated with symptom severity in the patients. This study postulated that the differences in ACC activation between patients and healthy participants could represent a stable vulnerability factor for the development of OCD. At a general level, patients with OCD might have a greater sensitivity to errors, manifest as a larger BOLD signal. This greater sensitivity could also lead to a greater tendency to perceive errors, even where behavior was correctly executed. This study also suggested that the OCD patients might tend to exhibit exaggerated affective response to errors (74).

Maltby et al (75) hypothesized that the exaggerated or false error signals generated by the ACC might underlie compulsive behaviors by triggering the feeling that things are 'not just right' even when no actual error has been made. In this fMRI study (75), participants were presented with a series of Go stimuli ('X's') and No Go stimuli ('K's') while being scanned. Participants were instructed to respond 'as quickly and accurately as possible' with a button press to Go stimuli and to inhibit responding to No Go stimuli. The proportion of

Go to No Go stimuli was 5:1 causing a prepotent bias toward Go stimuli and strong response conflict when No Go stimuli were presented. This task helped to analyze errors of commission (responding to No Go stimuli) as well as correct rejects (correctly inhibiting a response to No Go stimuli). During errors of commission and correctly rejected, high conflict trials, both rostral and caudal ACCs were hyperactive among OCD patients. The findings suggested that action-monitoring dysfunction in OCD may involve several other regions including lateral OFC, LPFC, posterior cingulate, and, for trials that involve inhibiting a prepotent response, basal ganglia and thalamus. Moreover, the findings suggested that the compulsive behaviors represent a failure to inhibit responding rather than a failure to properly complete a response. These findings are supported by a recent fMRI study in which OCD patients showed under-activation of fronto-striatal-thalamic-cortical circuitry during response inhibition. Results suggest that the thalamus and related circuitry may play a role in the expression or intensity of OCD symptoms, whereas right frontal sub regions may be involved in the suppression of symptoms (76).

fMRI studies have facilitated the understanding of the intriguing but consistently demonstrated spatial working memory deficits in OCD. van der Wee et al (77) assessed the performance of OCD patients on a parametric spatial n-back task. OCD patients performed poorly at the highest level of task difficulty and engaged the same set of brain regions as the matched healthy controls. In this set, the effect of difficulty on magnitude of brain activity was the same in patients and in controls except for a region covering the anterior cingulate cortex. In this region activity was significantly elevated in patients with OCD at all levels of the parametric task. These findings did not

support a deficit of the spatial working memory system proper, but suggest that the abnormal performance pattern may be secondary to another aspect of executive dysfunctioning in OCD (77). This proposition is supported by another study demonstrating improvements of spatial working memory deficits in OCD patients after treatment only in responders. Moreover, this improvement was associated with a change in the overall pattern of brain activity during the task (78). Various other fMRI studies have supported abnormalities of the OFC (79-81), insula (82), amygdale (83) and hippocampus (84) in OCD.

In a study examining the neural correlates of various symptom dimensions in OCD (46), patients demonstrated significantly greater activation than controls in bilateral ventromedial prefrontal regions and right caudate nucleus (washing); putamen/globus pallidus, thalamus, and dorsal cortical areas(checking); left precentral gyrus and right orbitofrontal cortex (hoarding); and left occipito-temporal regions (aversive, symptom-unrelated). The findings suggest that different obsessive-compulsive symptom dimensions are mediated by relatively distinct components of fronto-striato-thalamic-circuits implicated in cognitive and emotion processing (46).

An fMRI study examine the OCD patients in comparison with panic disorder as well as hypochondriasis patients to elucidate the disorder-specific neuroanatomical correlates of attentional bias using stroop as well as emotional stroop tasks. The study findings suggested increased distractibility for irrelevant information in patients with OCD, panic disorder, and hypochondriasis associated with frontal-striatal and limbic involvement. Although patients with OCD did not display an attentional bias in behavior

relative to controls, there was a clear, specific neural response during color naming OCD-related words, involving mainly ventral brain regions. In contrast, generalized emotional interference effects were found in PD and hypochondriasis, involving ventral and widespread dorsal brain regions, reflecting not only unconscious emotional stimulus processing but also increased cognitive elaboration. Thus, the brain activation pattern with relevance to stimuli might assist in differentiating OCD from other disorders like panic disorder and hypochondriasis (85).

Neurochemical Brain Imaging Studies

Magnetic Resonance Spectroscopy (MRS) measures concentrations of brain metabolites, such as N-acetyl-l-aspartate (NAA), combined glutamate and glutamine (Glx), myo-inositol (mI), choline (Cho), and creatine (Cr), in brain tissue. Studies comparing OCD patients with healthy controls using MRS research have reported that individuals with OCD showed decreased levels of NAA in the left and right striatum and the medial thalamus, as well as increased Glx in the caudate (86, 87) and also reduced NAA/Cr ratio as well as decreased glutamate in the anterior cingulate cortex of OCD patients. A recent studying combining fMRI as well as MRS has shown decreased NAA in dorsal ACC which correlated inversely with the blood-oxygen-level-dependent activation. This suggested that the ACC hyperactivity might be a compensatory response to this neuronal deficit (88).

MRS studies have examined neurochemical abnormalities with relevance to treatment. A recent MRS study by Mohamed et al (89) attempted to differentiate OCD patients who respond versus those who do not respond to pharmacological treatment (responders versus non-responders). Significantly

lower N-Acetyl Aspartate/Creatine ratios in the right basal ganglia in non-responders than in responders or in controls and higher Choline/Creatine ratios in the right thalamus in non-responders than responders. This study suggested that abnormal neuronal metabolism in the right basal ganglia and right thalamus may be indicating lack of response to treatment to selective serotonin reuptake inhibitor. Another study suggested that low N-Acetyl Aspartate levels in the cingulate cortex are found in OCD patients who responded well to selective serotonin reuptake inhibitor and atypical antipsychotic combination (90). Another longitudinal MRS study reported significantly higher glutamate concentrations in the left caudate nucleus of paediatric OCD patients which decreased significantly following treatment with paroxetine (91). Importantly, decrease in caudate glutamate levels had a significant positive correlation with reduction in OC symptoms. This study suggested that paroxetine might work by serotonergically modulated reduction of glutamate levels in caudate.

White Matter Abnormalities in OCD

Earlier studies examining the white matter in OCD used morphometric measurements and reported inconsistent findings (briefly reviewed in 92). Diffusion tensor-imaging (DTI) is a non-invasive technique allowing the in vivo examination of the white matter fibre tract integrity through fractional anisotropy (FA). This method is potentially more sensitive to detecting subtle and early changes in the microstructure and organization of white matter fibre tracts. Szeszko et al (93) showed, in comparison to healthy controls, fractional anisotropy was lower bilaterally in the anterior cingulate gyrus white matter and the parietal region, right posterior cingulate gyrus, and left occipital lobe in medicated patients with OCD. Cannistraro et al (94) have demonstrated

significantly high fractional anisotropy in the anterior limb of the internal capsule as well as the cingulum bundle in patients with OCD. A recent study by Yoo et al (92) increased FA in the corpus callosum, the internal capsule and white matter in the area superolateral to the right caudate. The increases in fractional anisotropy were mostly no longer observed in patients after 12 weeks of treatment compared with controls. This suggested that white matter alterations are associated with the pathophysiology of OCD and the abnormalities may be partly reversible with pharmacological treatment.

Electrophysiological Studies in OCD

Electrophysiological studies in OCD offer compatible findings along the lines of neuropsychological as well as other neuroimaging studies. These studies have demonstrated impaired response inhibition (95), pronounced error-related negativity (96), executive dysfunction (97), hypoactive sensory gating (98) and cingulate as well as fronto-parietal abnormalities (99). Interestingly, OCD patients have been reported to have sleep-onset REM periods (100) and this was associated with more severe symptoms. A longitudinal quantitative electroencephalogram studied demonstrated electrophysiological abnormalities to decrease after treatment with paroxetine in tune with previous PET studies (101).

OCD and Neurodevelopmental Abnormalities

Though OCD is often episodic, with stress related exacerbations followed by partial remissions, there is a group of patients whose illness follows a chronic deteriorating course. These patients are more likely to be men, with an early age of illness onset, and comparatively severe symptoms. This is consistent with the predominance of males among childhood onset OCD, and

the lower age of first admission and poorer outcome in males who develop OCD as adults (see for review, 102). Children with OCD are also more likely to show neurological signs than adults, with 80% exhibiting tics, and one-third displaying choreiform movements. Neurological soft signs such as involuntary movements, mirror movements and disturbed fine motor coordination have been demonstrated in OCD (103). OCD patients with high soft sign scores had significantly increased ventricular volumes compared with OCD patients with low soft sign scores and control subjects. These data suggest the existence of a subgroup of patients, characterized by male sex, early onset, severe symptoms, neurological signs, and a chronic course. This putative form of OCD thus bears some resemblance to neurodevelopmental disorders such as autism, dyslexia, and attention deficit disorder which has been termed as 'neurodevelopmental OCD' (102).

Brain Abnormalities in OCD: Summary

Neuroimaging studies suggest that the predominant pathogenesis in OCD might be secondary to fronto-striato-thalamo-frontal dysfunction (with related disturbances in the various other connecting brain regions like limbic system). ACC and OFC aberrations might potentially influence the fine balance between the direct and indirect striato-pallidal pathways. The direct pathway facilitates the execution of routines whereas the indirect pathway mediates inhibitory and switch function. In OCD, the former might be hyperactive and latter hypoactive. The resultant behavior is that certain routines are executed repetitively in response to enhance anxiety in the context of 'something is wrong' feeling.

Other Neurobiological Studies in OCD

Elucidation of the micro-architectural bases for these brain & behavioral

abnormalities has been attempted using additional neurobiological research paradigms namely neurochemistry, neuroimmunology and neurogenetics. The following sections attempt a brief overview of these studies (comprehensive reviews of these studies have been provided in some of accompanying chapters in this book).

Neurotransmitter Abnormalities in OCD

Serotonin

It is suggested that serotonergic abnormalities may play an important role in OCD (104-106). This is supported by the observed differential efficacy of serotonergic reuptake inhibitors in alleviating OC symptoms (107). While the selective serotonin reuptake inhibitors are found to be efficacious in OCD, selective noradrenergic drugs (for example desipramine) are not effective. The anti-OCD effect is mainly mediated by serotonegric mechanisms (see for review, 106).

Positron Emission Tomography studies have shown an increased metabolic activity in brain circuit involving the involving the orbitofrontal cortex (OFC), the head of the caudate nucleus, and the thalamus (108, 109). A successful treatment (pharmacological or behavioural) is associated with a normalization of their metabolic activity. Furthermore, provocative stimuli that induce OCD symptoms increase regional cerebral blood flow in the OFC and the head of caudate nucleus (for review, see 110).

Studies on the effects of SSRIs on presynaptic 5-HT1D autoreceptors in brain regions involved in OCD suggest that the autoreceptors in the OFC might be different in i) requiring higher SSRI dose as well as ii) longer latency

for desensitization. This is consistent with the common clinical observation that high doses of SSRIs are sometimes necessary to obtain an anti-OCD effect, and with the results of some fixed-dose double blind trials showing a dose-dependent therapeutic effect of SRIs. While the pre-synaptic receptors, the postsynaptic 5-HT2 like receptors remain normo-sensitive. It is thus likely that the activation of normosensitive postsynaptic 5-HT2-like receptors mediate the effect of the enhanced 5-HT release in the OFC (106).

Recently, 5-HT_7 receptor has also been implicated in the pathogenesis of OCD. It was observed that inactivation of the 5-HT_7 receptor leads to decreased burying behavior in the marble burying test, a model linked to OCD and anxiety, a finding that is also mimicked in wild-type mice after treatment with a selective 5-HT_7 receptor antagonist. The results strengthen and extend the hypothesis that antagonism of the 5-HT_7 receptor might be a valuable approach for the treatment of disorders, such as major depression and OCD, currently treated with antidepressants (111).

Glutamate

According to Carlsson (112), OCD is considered to be a hyperglutamatergic state involving prefrontal brain regions. Modulation of glutamate may play a role in the amelioration of OC symptoms by Selective Serotonin Reuptake Inhibitors (SSRI) and clomipramine (see for review, 112). Molecular biology studies (113) and magnetic resonance spectroscopy (114) also supports glutamatergic dysfunction in OCD. Moreover, several psychotropics that modulate glutamate (for example topiramate and riluzole [115]; D-cycloserine [116] have demonstrated to be useful in treating resistant OCD.

Dopamine

Several lines of evidence from preclinical and clinical investigations implicate dopamine in the mediation of certain types of repetitive behavior (117). Marazziti et al (118) have shown dopamine and serotonin abnormalities in patients with OCD. The behavior of rats treated chronically with the dopamine agonist, quinpirole, meets the ethological criteria of compulsive checking in OCD (119). Trials of combined SSRI and typical and atypical (see for review, 120, 121) antipsychotic treatment suggest that dopamine receptor antagonism may further reduce OC symptom severity in SSRI-refractory OCD patients, particularly those with comorbid tic disorders. It may be that some forms of OCD are associated with dysregulated dopaminergic function

.

Other Neurochemical Abnormalities in OCD

Studies have emphasized the role of neuropeptides (oxytocin, vasopressin, somatostatin and similar others) in the pathogenesis of OCD (122). Myoinositol is another hypothesized neuromolecule to play a role in the pathogenesis of OCD (123).

Neuroimmunological Studies in OCD

Work on the neuroimmunology of OCD comprises some of the most exciting research on the neurobiology of OCD (124, 125). This work can be traced back to early case reports of obsessive-compulsive symptoms in patients in whom Sydenham's chorea had developed in the aftermath of a streptococcal infection. Patients with Sydenham's chorea had a high prevalence of OCD. This work was of interest given that Sydenham's chorea may involve an autoimmune response in which antibodies to the basal ganglia develop.

Obsessive-compulsive symptoms can be precipitated or exacerbated simply by streptococcal throat infection. To describe such patients, the term pediatric autoimmune neuropsychiatric disorder associated with Streptococcus (PANDAS) was coined. Patients with OCD precipitated by streptococci may initially have increased basal ganglia volume, perhaps with subsequent loss of volume. Also, such patients may respond to specific immunologic interventions, such as plasmapharesis or intravenous immunoglobulin therapy. Of further interest in this regard is a body of work showing that patients who expressed a particular B-lymphocyte antigen, known as D8/17, are more susceptible to poststreptococcal autoimmune sequelae (see for review, 124, and 125).

Genetics of OCD

Over the past two decades, the interest in genetic mechanisms underlying many psychiatric disorders has resurged. The changes in the understanding of OCD reflect this shift of perspective. Twin studies and family studies strongly suggest that vulnerability to OCD can be inherited (126), but a positive family history is absent in many patients. Older studies of monozygotic twins show a 65% concordance for OCD, but no control groups were included. One study found an 87% concordance for 'obsessional features' in monozygotic twins; the concordance of dizygotic twins was only half as large. On the other hand, none of the eight monozygotic twin pairs in another study were concordant for OCD (see for review 127). These study results support the theory that specific environmental (non-shared) and genetic factors are important for the manifestation of behaviors seen in OCD. Biological components are indicated as being potentially important in the cause of OCD, but none of these studies provided conclusive evidence. Also important methodological limitations

were present, including a lack of standardized diagnostic criteria across studies, small sample sizes, and a lack of procedural blind methods for obtaining diagnostic information or for making actual diagnoses. All of these limitations increase the risk for inflating the concordance rates and yielding type 2 (i.e., false-positive) errors.

Many studies examined the association between OCD and a functional polymorphism of the serotonin transporter gene promoter (5-HTTLPR) but yielded inconsistent results. A recent meta-analysis showed that OCD was found to be associated with the SS homozygous genotype, but was inversely associated with the LS heterozygous genotype. No association with the LL homozygous genotype or the allelic distribution was found. These results suggest that variations of the serotonin transporter gene influence the risk of OCD, but their functional roles in the pathogenesis of OCD need to be elucidated (128). The relationship between dopamine as well as glutamate system related genes has been comprehensively reviewed in an accompanying chapter in this book.

A study examining a sample of 34 European-American family trios (proband and both parents) for linkage disequilibrium between OCD and the SLC6A4 promoter polymorphism reported a statistically significant association between the 'long' form of the promoter and OCD. Another study used the candidate gene approach to test for an association between a functional allele of the catechol - O - methyltransferase (COMT) gene and OCD showed association between low COMT enzymatic activity and OCD, together with evidence for a similar sexually dimorphic association between OCD and an allele of the MAO-A gene (see for review, 129). Another recent

study by Pooley et al (130) concluded that COMT may play a role in the genetic aetiology of OCD in men. The biological plausibility of the association is increased by the functionality of the val158met polymorphism in terms of its effect on COMT enzyme activity, and by the role of COMT in cortical dopamine signalling and information processing (130).

It has been found recently that an antigen, which is a genetic marker for rheumatic fever susceptibility, is also a marker for susceptibility to an autoimmune form of childhood-onset OCD. This B lymphocyte cell surface antigen recognized by the D8/17 monoclonal antibody is a genetic marker for susceptibility to rheumatic fever. This marker is significantly more common in children with OCD or tic disorders, with or without associated Sydenham's chorea, than in matched controls (131).

Another recent pioneering study showed that mice with genetic deletion of Sapap3 exhibit increased anxiety and compulsive grooming behaviour leading to facial hair loss and skin lesions; both behaviours are alleviated by a selective serotonin reuptake inhibitor. Electrophysiological, structural and biochemical studies of Sapap3-mutant mice reveal defects in cortico-striatal synapses. Furthermore, lentiviral-mediated selective expression of Sapap3 in the striatum rescues the synaptic and behavioural defects of Sapap3-mutant mice. These findings demonstrate a critical role for SAPAP3 at cortico-striatal synapses and emphasize the importance of cortico-striatal circuitry in OCD-like behaviours (132). Some of the other novel genes that are implicated in OCD are extra neuronal monoamine transporter gene (133), glutamate tranporter gene (134), oligodendrocyte lineage transcription factor 2 gene (135) and NrCAM gene (136).

The next step in understanding the genetics of OCD is the localization and characterization of the genes that confer susceptibility. These genetic methods must be combined with careful clinical and epidemiologic work to correctly elucidate the cause of OCD. Future research also should define subsets of endophenotypes of the disorder. Factors such as brain abnormalities, neuropsychological functioning, comorbidity, and age of onset are extremely useful in the continued study of genetic mechanisms involved in the cause of OCD.

Summary of Other Neurobiological Studies in OCD

Neurotransmitter studies in OCD implicate predominantly serotonin, dopamine and glutamate abnormalities in OCD with support from genetic studies demonstrating association with the relevant genes. These neurotransmitter systems are intricately linked with fronto-striato-thalamo-frontal circuitry. Moreover, neuroimmunological studies suggest immune alterations targeted towards basal ganglia might underlie OCD symptom genesis in some patients. Thus, these additional neurobiological findings also support fronto-striatal dysfunction in OCD.

Neurobiology of OCD: The Way Ahead -Quo Vadis?

Most work on the neurobiology of psychiatric disorders focuses on proximate mechanisms (e.g., brain / neurotransmitter / gene dysfunction) responsible for these conditions. However, evolutionary theory also raises questions about the distal mechanisms that are involved in pathogenesis or the evolutionary history behind the development of different dysfunctional phenotypes (see for review, 124).

OCD involves several behaviors that might well have been conserved

during the course of evolution. Members of a range of species, including primates, have genetically inherited motoric and cognitive procedural strategies (i.e., fixed action patterns, learned habits, or response sets) that contribute to checking for danger, reducing contamination, and hoarding (mostly of food). An immediate hypothesis would be that dysfunction of any of these inherited programs may lead to OCD. Certainly, evidence shows that the basal ganglia are a repository for species-specific procedural strategies.

Such a hypothesis would be strengthened by the description of disorders analogous to OCD in other species. Several such conditions may exist. Perhaps the best characterized of these, and arguably the most reminiscent of OCD, is canine acral lick dermatitis. This disorder is characterized by excessive licking or biting of the extremities, which leads to localized alopecia and subsequent granulomatous lesions. A range of behavioral and medication interventions have been tried, but of interest to work on OCD are reports that SSRIs are successful. It has been demonstrated that acral lick dermatitis responds more robustly to clomipramine than to desipramine (see for review, 124).

From evolutionary perspectives, the OFC abnormalities support a role for the 'Somatic Marker Hypothesis' proposed by Damasio (137, 138), which speculates that the link between external stimuli and internal states is modulated by the function of the OFC. According to this hypothesis, when an individual faces a decision, each alternative elicits a physiological state that corresponds to an emotional reaction. This 'marker' signals act at multiple levels of operation: some occur overtly (consciously) and some occur covertly (imperceptibly or unconsciously). The marker signals arise in bio-regulatory processes that are related to emotions and feelings but also to the physiological

state structure and regulation. Hence, these markers are termed 'somatic' i.e., they relate to body-state structure and regulation even when they do not arise in the body proper but rather in the brain's representation of the body. Examples of the covert action of 'marker' signals are the undeliberated inhibition of a response learned previously; the introduction of a bias in the selection of an aversive or appetitive mode of behaviour, or in the otherwise deliberate evaluation of varied option-outcome scenarios. Examples of overt action include the conscious 'qualifying' of certain option-outcome scenarios as dangerous or advantageous. The somatic marker hypothesis provides an account of deficits in decision-making, positing that they are the result of defective activation of somatic markers that normally function as covert or overt signposts for helping to make advantageous choices. In other words, optimal functioning of these 'somatic markers' might have had some survival advantages in ontogeny and / or phylogeny. While the applicability of the 'somatic marker hypothesis' has been elucidated to some extent with relevance to the proximal etiology (for example, deficits in neuropsychology, neural circuitry, neurotransmitter and neurogenetics) the relationship with distal etiology (i.e., the evolutionary basis) is yet to be explored.

Conclusions & Future Directions

Review of neurobiological studies suggests strong evidence for abnormalities involving various domains namely the neuropsychology, brain structure and function, neurophysiology, neurochemistry and neurogenetics. These neurobiological abnormalities merge coherently with certain predictions that could be made by a careful clinical examination of the phenomenology of OCD. Such intuitive clinical predictions are supported by studies that suggest OCD patients to have the following deficits such as:

(i) attention impairments (due to the 'intrusiveness' of OC symptoms)

(ii) memory / metamemory impairment (when OCD patients forget doing certain activities, eg. locking the door)

(iii) error monitoring (caused by the enduring 'something is wrong' feeling)

(iv) emotion processing, motivation-reward systems and response inhibition (because of the tendency of these patients to persist with compulsions because of the 'short-term' rewards).

Consistent with this, neuroimaging studies suggest that the predominant pathogenesis in OCD might be secondary to fronto-striato-thalamo-frontal dysfunction (with related disturbances in the various other connecting brain regions like limbic system). Hyperfunctional anterior cingulate cortex might result in decreased threshold for error detection and can lead to enhanced perceived personal responsibility. Along with this, aberrance in orbitofrontal cortex might lead to impaired response inhibition. Together this dysfunction might potentially influence the fine balance between the he direct and indirect striato-pallidal pathways. The direct pathway facilitates the execution of routines whereas the indirect pathway mediates inhibitory and switch function. In OCD, the former might be hyperactive and latter is hypoactive. The resultant behavior is that certain routines are executed repetitively in response to enhance anxiety in the context of 'something is wrong' feeling. The neurochemical and genetic basis for the manifestations seems to involve predominantly serotonin, dopamine and glutamate systems and perhaps many other neurotransmitters systems as well. While neuroimmunological studies might explain the occurrence of OCD in a select subset (eg. PANDAS), the majority requires further systematic elucidation.

Future studies should attempt to utilize combination of neurobiological research techniques to examine relatively more homogeneous subgroups of OCD. While neurodevelopmental abnormalities in OCD suggest aberrant ontogeny, the phylogenic significance of OCD is another interesting and potentially fruitful line of research approach which might offer a 'theory-driven' research. Optimal application of cutting edge neurobiological research techniques combined with 'distal mechanism' focussed **h**uman **o**ntogenic & **p**hylogenic **e**volutionary studies offer **hope** that one might perhaps be able to unravel the mystery of OCD at some point in time.

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Chapter 4

Genetics of OCD: Current Understanding andFuture Directions

V. Eapen

Introduction

Obsessive-Compulsive Disorder (OCD), affecting 1-2% of the population is characterized by obsessions which are intrusive thoughts and impulses, and by repetitive compulsive behaviors. The pendulum regarding the etiologic theory of OCD has swung from being considered as a manifestation of psychodynamic conflict throughout most of the twentieth century, to that of a neuropsychiatric illness with an underlying neurobiological abnormality. This has been particularly true in the last two decades. Treatment advances, brain imaging studies and results of pharmacological challenges have redefined etiologic theories and generated new research paradigms. While the response of OCD symptoms to pharmacological agents and the neuroimaging findings that specific regions of the brain may be involved in OCD suggest a biologic etiology, family studies have pointed towards a genetic etiology.

A genetic etiology has been suggested for OCD on the basis of several factors including

1) twin studies with a higher concordance rate among monozygotic (MZ) twins than dizygotic (DZ) twins
2) a higher incidence among the biological offsprings of affected individuals even when they have been adopted away and reared in

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adoptive homes where the adoptive parents have been unaffected

3) family studies showing a significant aggregation of the illness within families when compared to the population prevalence
4) segregation analysis providing support for a major gene, and
5) linkage and association studies revealing promising candidate genes.

Twin Studies

A review of studies in OCD on twin pairs has suggested a concordance rate of around 50% to 60% (1). Using the Maudsley Twin register, Carey & Gottesman (2) reported the rate among 15 MZ twin pairs for OC features to be 87% as compared to 47% in 15 DZ twin pairs. In a study of 419 pairs of twins using the Leyton Obsessional Inventory, heritabilities of 44% for OC traits and 47% for OC symptoms were reported (3). Inouye (4) reported 80% concordance rate for "obsessional neurosis" among ten pairs of Japanese MZ twins, while the concordance rate for four pairs of DZ twins was 50%. In another study, McGuffin and Mawson (5) reported that identical twin pairs who were separated prior to the onset of OCD symptoms were not aware of each other's problems. Despite this, the OC symptoms were noted to start at similar ages and followed a similar course in both pairs. Two other studies on twins have suggested that, whilst genetic factors are important for anxiety disorders in general, this contribution is obscured by the grouping of anxiety symptoms into specific disorders (6, 7). In this regard, it is interesting to note that pharmacological response to clomipramine (8) and sertraline (9) has been found to be similar in MZ than DZ twins. In the most recent review of twin researches by Van Grootheest et al (10), it was observed that only the studies that used a dimensional approach and analyzed the data with Structural Equation Modeling have convincingly shown that OC symptoms are heritable

in children, with genetic factors accounting for 45% to 65%. Similar studies in adults suggest that the genetic influence on OC symptoms range from 27% to 47%. On a similar vein, Jonnal et al (11) in a study of 527 twin pairs using the self-report Padua Inventory of OC symptoms found heritabilities of 33% and 26% for obsessions and compulsions respectively. Thus, while the data from Twin studies support a genetic basis for OCD, it should be noted that in all twin data reported, the concordance for MZ twins was less than 1.0 and heritability estimates were consistently less than 1.0 suggesting that while genetic factors are important, these behaviors are also influenced by environmental factors. In this regard, an analysis of OC traits by Cox et al (12) showed a strong interaction between genetic and environmental factors.

Family Studies in OCD

A review of family studies in OCD suggest significantly higher rates in parents and siblings of OCD probands with an age corrected morbid risk of around 35% in first degree relatives (FDRs) (13). In the 1930s, Lewis et al (14) reported a rate of 32.7% OC traits in a sample of 306 FDRs. Several family studies since then have reported significantly higher rates of OCD in parents and siblings of OCD probands, with rates among parents being 5 to 10 times higher, when compared to population prevalence estimates (15). Rasmussen and Tsuang (1) found that 4.5% of parents of OCD patients met the full criteria for OCD as per DSM-III, while an additional 11.4% had probable OCD or OC traits. Lenane et al (16) in a study of 145 first degree relatives of 46 children and adolescents with OCD found an age corrected morbid risk of 35% in first degree relatives for OCD and subclinical OCD. Riddle et al (17) in a clinically referred sample of children with OCD observed that 71% had a parent with either OCD or OC symptoms.

Other studies have examined the role of genetic factors in anxiety disorders in general, and have suggested that an anxiety disorder diathesis is transmitted in families with OCD but that its expression within these families is variable (6,7) . In this regard, Black et al (18) studied FDRs of 32 adult probands and 33 psychiatrically normal controls. They found that the morbid risk for anxiety disorders was increased among the relatives of OCD subjects when compared to the relatives of controls, but the risk for OCD was not. Risk for a broadly defined OCD was increased among the parents of OCD probands but not among the parents of controls (16% vs 3%).

Bellodi et al (19) using 21 OCD patients with an age at onset of less than 14 years observed the morbidity risk to be 8.8% among FDRs of these probands, as compared to 3.45% among the relatives of 71 later-onset probands. Similarly, Pauls et al (20) found the rates among FDRs of OCD probands to be 10.3% for OCD and 7.9% for subthreshold OCD as compared to 1.9% and 2.0% respectively for control subjects. Nestadt et al (21) also reported similar rates of 11.7% among FDRs of OCD patients as compared to 2.7% for control subjects. A study by Fyer et al (22) noted a significantly higher risk for OCD but not for other anxiety disorders, and a subsequent study by the same group (23) found evidence of familial OCD only when the diagnostic threshold was lowered to include cases with probable OCD or OCD symptoms.

OCD has also been linked to Tourette Syndrome (TS), with the suggestion that OCD forms an alternative phenotypic expression of TS (24, 25). Pauls et al (20) in a family study demonstrated that the frequency of OCD in the absence of tics among first degree relatives was significantly elevated in

families of both TS+OCD and TS-OCD probands, and that these rates were increased over estimates of the general population and a control sample of adoptive relatives. Studies examining the relationship between age of onset of OCD in probands and their affected relatives have found that childhood onset OCD is a highly familial disorder and that these early onset-cases may represent a valid subgroup, with higher genetic loading and shared vulnerability with chronic tic disorders (26). The study by Bellodi et al (19) as well as The Hopkins OCD Family Study also suggested that earlier age of onset is associated with greater familiality. Further support for this notion comes from the study of Hemmings et al (27), who found a clinical association between early age of onset and an increased frequency of tics and related disorders. They also demonstrated a genetic association between early onset OCD and the dopamine receptor type 4 gene (DRD4) suggesting a role for dopaminergic system in the development of early-onset OCD, unlike the serotonergic system that is implicated in adult OCD.

Studies examining the comorbidity of OCD with tic disorders may also serve to define important clinical subtypes with different phenomenology and neurobiological mechanisms (28). In a family study of OCD probands and TS+OCD probands, Eapen et al (29) found that all the OCD probands who shared a similar symptom profile to that of TS probands had at least one first degree relative with OCD, while none of the probands from the other group had a positive family history. These authors concluded that the latter could be regarded as sporadic or non-familial cases. In a cluster analysis study, Lochner et al (30) identified three separate clusters at a 1.1 linkage distance level, but found that none of these clusters were associated with any particular genetic variant. The lack of genetic validation of these clusters may again indicate the

clinical and genetic heterogeneity in OCD and the involvement of other, as yet untested, genes.

Familial basis of different clinical symptom dimensions have been suggested. Bhattacharyya et al (31) suggested familiality of checker subtype in a family study. Denys et al (32) in a factor analysis study identified five consistent symptom dimensions (contamination and cleaning; aggressive, religious and sexual obsessions; somatic obsessions and checking; symmetry, counting/arranging compulsions; and high-risk assessment checking) with significant differences in gender distribution, age of onset, and familial prevalence of OCD. Yet another study by Leckman et al (33) also found evidence for symmetry/ordering as well as obsessions/checking to have dominant major gene effects in a TS sample with OCD. These findings suggest that these may constitute genetically significant subtypes of OCD. In this regard, three subtypes of OCD have been described 1) familial OCD, 2) familial OCD linked to TS and tics, and 3) non familial OCD(28). These observations may be consistent with genetic heterogeneity within both OCD and TS (34).

Segregation Analysis

Once twin studies have suggested possible genetic transmission (heritability), and family studies have suggested higher recurrence risk to relatives, segregation analysis can determine whether the patterns within families are consistent with genetic models. Using computer programs (e.g. SEGRAN, POINTER), different genetic models (dominant, recessive, mixed, polygenic etc.) are examined and the hypotheses are tested using likelihood ratio test (LRT), by estimating the difference in values of (-2ln (L) + k) where L

= likelihood ratio and k = a constant, for a specific hypothesised model. The best fitting model is assigned a value of 0.0, and all other models are expressed as positive deviations from the best model. Evidence for a major locus component is assessed by comparing the given model to that of mixed model (including both major locus and polygenic components) in which the major locus has been removed; i.e. determining whether the hypothesis of 'no major locus component to transmission' can be rejected.

Segregation analysis by Nicolini et al (35) in 24 families of OCD, Chronic Motor Tics (CMT) and TS subjects suggested a dominant pattern of inheritance with 80% penetration. The segregation ratio in the normal, by normal parental mating type was 0.33+/- 0.16 and 0.39+/- 0.14 in the normal by affected parental mating type. In yet another segregation analysis study of OCD families, Cavallini et al (36) carried out segregation analysis on a sample of 107 OCD families and observed a dominant model of transmission with a higher penetrance for females. Alsobrook and colleagues (37) in a segregation analysis study using factor-analytic symptom dimensions to subset the family sample based upon probands' symptom factor scores, found that families high in symptom score of symmetry and ordering had a higher risk of OCD in the relatives. Although they could not identify a specific Mendelian model, analyses limited to families' probands with high symmetry and ordering symptoms led to rejection of the polygenic model, indicating the involvement of a major locus model. Similarly, Nestadt et al (21) using 153 families (80 cases and 73 controls) from The Hopkins study showed a best fit dominant model with heterogeneity by gender, with stronger transmission in females. Hanna et al (38) using 52 families (35 cases and 17 controls) of childhood OCD probands aged 10 to 17 years found evidence for a major susceptibility

locus in families with OCD when age at onset was incorporated into the model. Eapen et al (39) performed segregation analysis using data from 66 FDRs ascertained through 20 families of OCD probands and suggested evidence for a major locus mode of transmission in OCD.

Thus, while available evidence from segregation analysis studies suggests that the familial transmission of OCD is genetic in origin, the exact mode of transmission is still unclear. While some studies have suggested a possible dominant model, a mixed model involving several genes of major effect on a multigenetic background cannot be ruled out.

Linkage Studies

Once the familial transmission through genetic mechanism is established, the next step would be to perform linkage analysis to locate putative major gene loci within chromosomal segments or 'hot spots'. This is based on the assumption that loci that are situated close together on the same chromosome are transmitted together (linked). Linkage analysis is based on meiotic events which determine whether contiguous genes will remain on the same chromosome through recombination. If the genes become separated through recombination, that is indicative of cross over having occurred. The probability of cross over for two genes or a putative gene and a marker is a function of the distance between them. This is calculated using a map of signals throughout the genome that reflect the distance between the putative gene locus and a known marker. The likelihood ratio of linkage/no-linkage or odds of linkage is then calculated and the odds ratio is expressed by the LOD score or the log of the odds ratio. A LOD score of 3 [odds of 1: 1000 (log odds =3)] is taken as significant for accepting the linkage hypothesis and -2.0 as the

cut off for rejecting linkage. It is to be borne in mind that although 3 is considered as a cut off for Mendelian loci, this may not be sufficient for more complex disorders.

Weissbecker et al (40) reported a LOD score of 1.3 in the 4p13 chromosome region in a three-generation family with OCD and tics. Hanna et al (38) studied 56 individuals from 7 families ascertained through childhood OCD probands and found multipoint linkage on chromosome region 9p24 with a LOD score of 2.25 while using an average inter-maker distance of 11.3cM. When an average spacing of 1.6 cM was used, the LOD score dropped to 1.97 and with non-parametric methods yielded a LOD score of 1.73. This result was replicated by Willour et al (41) on 50 OCD pedigrees using parametric and nonparametric analyses with microsatellite markers spanning the 9p24 candidate region. Shugart et al (42) in a genome-wide linkage study of 219 families ascertained through the OCD Collaborative Genetics study suggested evidence for susceptibility loci on chromosomes 3q, 7p, 1q 15q and 6q, with the strongest evidence being on 3q27-28. Furthermore, covariate-linkage analyses implicated a possible role of gene(s) on chromosome 1 in increasing the risk for an earlier-onset form of OCD.

Association Studies

While linkage analysis is used to demonstrate whether a DNA marker with a known chromosomal localization is transmitted together with the disease gene in families, association studies are used to ascertain the frequency of particular marker phenotypes in patients who have the disorder as compared to healthy controls. This is achieved by comparing the distribution of genotypes or alleles of genes implicated in the neurophysiology of OCD (candidate genes) using

family based or case-control association studies. In this regard, several candidate genes have been studied.

Serotonin

Evidence for the role of the serotonin (5HT) system in OCD primarily comes from the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD. The Serotonin Transporter gene (OMIM* 182138) on chromosome 17q12 is a target of SSRI action, which increases serotonin synaptic cleft bioavailability by decreasing SCL6A4 action. SCL6A4 has a functional biallelic polymorphism consisting of an insertion (long allele L) or a deletion (short allele S) in the promoter region (5HTTLPR). Several studies have therefore focussed attention on this candidate gene with some investigators suggesting an association of L allele with OCD, and others failing to find such an association (Table1). The 5-HT1Dß receptor gene (OMIM* 182133) with variants G861C (G to C substitution at nucleotide 861 of the coding region) and T371G, is another gene of interest in the context of OCD. While there is some evidence in favour of an association between 5-HT1Dß G861C allele polymorphism and OCD as well as that of 5-HT2A gene polymorphism and OCD, other studies have failed to replicate this finding (Table 2). Given the fact that tryptophan hydroxylase (TPH) is the rate limiting enzyme in the synthesis of 5-HT and hence influence serotonin turnover, TPH1 and 2 genes have been the subject of at least three studies (Table 3). While one study found a significant preferential transmission of the haplotype G-C to OCD, the other two studies yielded negative results.

Table 1 : Serotonin Transporter Gene

Sl. No.	Author (year)	Population	Main Findings
1.	Mc Dougle et al (43)	European - American	▪Association and linkage disequilibrium between 5-HTT linked the promoter region (5-HTTLPR) gene L allele with OCD. ▪Poor response to SSRIs may be related to L allele.
2.	Bengel et al (44)	Caucasian	OCD patients are more likely than controls (46.7% vs 32.3%) to carry two copies of the L allele.
3.	Kinnear et al (45)	Afrikaner	No significant association between the distribution of 5-HTTLPR genotypes and OCD.
4.	Camarena et al (46)	Mexican	No significant association between the L allele and OCD.
5.	Frisch et al (47)	Jewish	No significant association between the L allele and OCD.
6.	Walitza et al (48)	German	No significant association between the L allele and OCD.
7.	Chabare et al (49)	French	No significant association between the L allele and OCD.
8.	Kim et al (50)	Korea	▪No significant association between the L allele and OCD. ▪Patients with L/L + S/L genotype had higher scores on the religious/somatic factor of the Y-BOCS than those with S/S genotype. ▪Frequency of 5-HTTLPR genotype revealed higher percentage of S/S genotype (63 64%) and lower percentage (3%) of L/L genotype.
9.	Hu et al (51)	Mixed population of African, American, Finish & US White, American Plains Indians & Southwest Indians	▪Gain of function LA LA genotype was twice as common in whites with OCD. ▪The LA allele was overtransmitted to OCD probands by two fold.
10.	Dickel et al (52)	American	No evidence for association at serotonin system genes SLC6A4-5HTTLPR, HTRIB, HTRZA after statistical correction for multiple testing.

Table 2 : Serotonin Receptor Gene

Sl. No.	Author (year)	Population	Main Findings
1.	Enoch et al (53)	Caucasian	- 1438 A allele of the 5HT2 A frequency was higher in female OCD patients but not in male patients.
2.	Walitza et al (64)	German	▪Association between -1438A allele of the 5HT2A gene and childhood OCD. ▪No association between 5HT71Bß gene and OCD.
3.	Meira-Lima et al (4)	Brazilian	Association between C516T 5-HT 2A gene polymorphism and OCD.
4.	Tot et al (55)	Turkish	TT genotype for T102C and AA genotype for -1438 G/A polymorphism of 5HT2A are significantly higher in patients with severe OCD as compared to those with moderate to severe OCD.
5.	Hemmings et al (56)	Afrikaner	No association between -1438 A/G polymorphism or T102 polymorphism and OCD.
6.	Frisch et al (47)	Jewish	▪No association between -1438 A/G polymorphism and OCD. ▪No association between 5-HT2C receptor polymorphism and OCD.
7.	Nicolin et al (57)	Mexican	No association between 5-HT2C receptor polymorphism and OCD.
8.	Cavalline et al (58)	Italian	No allelic or genotypic association between OCD and 5-HT2C receptor gene
9.	Mundo et al (59) (60)	European-Caucasian (96.7%), Asian (3.3%).	G861 allele of the 5-HT1Dß gene is preferentially transmitted to OCD patients.
10.	Hemmings et al (56)	Afrikaner	No association between 5-HT1Bß gene and OCD.
11.	Lochner et al (61)	Caucasian-(South Africa)	No association between 5-HT1Bß gene and OCD.
12.	Camarena et al (62)	Mexican	No association between 5-HT1Bß gene and OCD.
13.	Di Bella et al (63)	Italian	No association between 5-HT1Bß gene and OCD.

Table 3 : Tryptophan Hydroxylase (TPH) Gene

Sl. No.	Author (year)	Population	Main Findings
1.	Frisch et al (47)	Jewish	No association between TPH1 and OCD.
2.	Walitza et al (48)	German	No transmission disequilibrium for alleles of SNPrs 1800532(TPH1 gene) in patients with early onset OCD
3.	Mossner et al (65)	German	A significant preferential transmission of haplotype G - C to OCD and a trend of preferential transmission of the C allele of SNPrs 4565946 to early onset OCD.

Dopamine

Studies on Dopamine Transporter gene (DAT1) suggest that DAT1 gene polymorphism is not likely to confer susceptibility to OCD (Table 4). Similarly, all the three studies that have examined the role of dopamine transporter gene DRD3 have failed to find any significant association with OCD (Table 5). On the other hand, there has been some evidence for the association of OCD with dopamine transporter gene DRD4 variant (Table 5).

Table 4 : Dopamine Transporter Gene (DAT1)

Sl. No.	Author (year)	Population	Main Findings
1.	Frisch et al (47)	Jewish	No association between DAT1 gene and OCD.
2.	Hemmings et al (66)	Afrikaner	No difference in the distribution of DAT1 VNTR between OCD and control subjects.
3.	Yoo et al (66)	Korea	No association between DAT1 gene and OCD.

Table 5 : Dopamine Receptor Gene

Sl. No.	Author (year)	Population	Main Findings
1.	Billet et al (67)	Canadian	Significant differences in allele frequencies between patients and controls for DRD4 gene.
2.	Frisch et al (47)	Jewish	No significant differences of genotype distributions of DRD4 between OCD and control subjects.
3.	Hemmings et al (56)	Afrikaner	No association between DRD4 gene and OCD.
4.	Millet et al (68)	French	▪Absence of transmission of 2-repeats allele of DRD4 gene (48 bp VNTR) in OCD. ▪Significantly lower frequency of 2-repeats allele in OCD than controls.
5.	Hemmings et al (60)	Afrikaner & South African Caucasian	Lower frequency of the DRD4 VNTR 7-repeat allele in early onset OCD than late onset OCD in South African Caucasians but not in Afrikaners.
6.	Kim et al (70)	Korea	▪Short genotype frequency of DRD4 was significantly higher in OCD patients than in normal control groups. ▪No difference in genotype frequency between early onset and late onset OCD.
7.	Denys et al (71)	Netherland	▪No significant differences in genotype distribution of DRD2 between OCD and controls. ▪Higher frequency of the DRD2 A2 allele in male OCD patients as compared to male controls.
8.	Nicolini et al (67)	Mexican	No association between Serq Gly variant of DRD3 gene and OCD.
9.	Billet et al (67)	Canadian	No association between Serq Gly variant of DRD3 gene and OCD.
10.	Catalard et al (74)	Italian	No association between Serq Gly variant of DRD3 gene and OCD.

COMT

Catechol-O-methyltransferase (COMT) is an enzyme involved in the inactivation of catecholamines namely adrenaline, noradrenaline and dopamine. Several studies have examined the role of COMT gene (OMIM * 116790) in OCD, with conflicting results (Table 6).

Table 6 : COMT

Sl. No.	Author (year)	Population	Main Findings
1.	Karayiorgou et al (75) (82)	Caucasian	Low activity allele (Met 158) at COMT locus is significantly associated with OCD in males only.
2.	Schindler et al (76)	Caucasian	Tendency for an association between homozygosity (Met/Met or (Val/Val) at the COMT locus and OCD.
3.	Alsobrook et al (77)	Caucasian	Mildly significant association with the low activity COMT allele in female probands of OCD but not in males.
4.	Niehaus et al (78)	Afrikaner	Heterozygous genotype (Val/Met) is significantly more common in OCD.
5.	Meira Lima et al (54)	Brazilian	No significant association between COMT gene and OCD
6.	Erdal et al (79)	Turkish	No significant association between COMT gene and OCD
7.	Ohara et al (80)	Japanese	No significant association between COMT gene and OCD

MAO

Monoamine oxidase A (MAOA) enzyme is involved in the metabolism of biogenic amines including noradrenaline, serotonin and to a lesser extent, dopamine. Of the two polymorphisms noted in MAOA gene (OMIM * 309850), one is designated as MAOA-uVNTR, and the other is a T to C substitution on exon14 designated as EcoRV, with the T allele being related to lower enzyme activity. Studies in OCD indicate the possibility of an association between the MAOA gene and OCD (Table 7), and in particular a sexually dismorphic effect of COMT and MAOA on genetic susceptibility to OCD (82).

Other genes

Studies on OCD have also focused on the role of other putative

Table 7 : MAO

Sl. No.	Author (year)	Population	Main Findings
1.	Camarena et al (81) (46)	Mexican	Low activity allele (Met 158) is significantly associated with OCD in males only.
2.	Hemmings et al (56) Cited in	Afrikaner	No association between ECO RV of the MAOA gene and OCD.
3.	Kim & Kim (82)	Korea	Higher frequency of 3-repeats of MAOA-UVNTR in male OCD patients than in normal male controls (47.8%).

neurotransmitters such as glutamate and gamma amino butyric acid (GABA) (83, 84, 85) and association studies have highlighted the role of genes involved in glutamatergic neurotransmission, and in particular the glutamate transporter gene SLC1A1 in 9p24 (86, 87). A recent study showed that targeted depletion of SAPAP3 in mice leads to a behavioural phenotype similar to OCD characterized by excessive grooming and anxiety (88). Since SAPAP3 is highly expressed in the striatum and functions as postsynaptic scaffolding protein at excitatory synapses, the defect appears to be in the glutamate responsive synapses.

Developmental genes such as Hoxb8 (Homeobox-containing complex) group of 39 transcription factors) that regulate positional information during development (89) as well as the brain derived neurotrophic factor (BDNF) that is involved in the apoptotic pathways of neuronal development (90) have also been implicated in OCD (Table 8).

Future Directions

Last decade has seen a rapid progress in our understanding of the genetic mechanisms involved in OCD, and according to the collective knowledge till

Table 8 : Other genes

Sl. No.	Author (year)	Population	Main Findings
1.	Arnold et al (83)	Glutamate	Association of N-methyl-d-aspartate 2B (GRIN2B) with a susceptibility to OCD.
2.	Delorme et al (84)	Glutamate	No association of glutamate receptor ionotropic kainate 3 (GRIK3) S301A or GRIK2 rs 2227281 (intron 14) and rs 2227283 (exon 15) with OCD but the GRIK2 SNP 1867 allele (rs 2238076) in exon 16 is transmitted less than expected in OCD.
3.	Zai et al (85)	GABA	Trend for an over-expression of the -7265A allele at the A-7265 G polymorphism in OCD.
4.	Arnold et al(86)	Glutamate (NMDA)	Glutamate (NMDA) subunit receptor gene SLC1A1/EAAC1 associated with OCD
5.	Dickel et al(87)	Glutamate transporter gene solute carrier family 1, member 1 (SLC1A1)	Association of OCD with polymorphisms in the 3' region of SLC1A1 in early onset OCD
6.	Welch et al (88)	Glutamate SAPAP3 (DLGAP3)	Association of OCD behaviour in mice with deletion of SAPAP3 gene
7.	Greer et al (89)	Hoxb8 (Homeobox-containing complex)	Association of OCD and trichotillomania with greater expression of Hoxb8.
8.	Hall et al (90)	BDNF (Brain Derived Neurotrophic factor)	Met 66 allele of the BDNF gene when undertransmitted confers a protective effect against OCD.

date, it is evident that OCD has a significant genetic component (91, 92, 93). However, not all cases of OCD appear to be familial, with suggestions that even in the familial form, the level of heterogeneity in OCD phenotype may be high. Combined epidemiological and family studies are of crucial importance at this juncture to address some of the issues related to the true estimates of the prevalence of OCD as well as the phenotypic subtypes. While segregation analyses point to the role of a major gene locus, genome-wide linkage studies have identified putative candidate genes. Future studies should include large

sample sizes and focus on

1) patients sub-typed on categorical basis such as early and late onset, related to tics or not, as well as on the basis of symptom dimensions such as OC personality trait
2) comorbidity with mood or anxiety disorders and link with TS, attention deficit hyperactivity disorder (ADHD), autism etc.
3) endophenotypes such as neuroimaging or neurophysiological findings
4) genotypic distribution based on gender, pharmacological response, and ethnicity.

In addition to such attempts to elucidate the issue of clinical and genetic heterogeneity, it is also important to understand the contribution of environmental factors that act as shared environment and/or biological triggers that influence the expression of the disorder.

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Chapter 5

Immunology of OCD

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Introduction

Obsessive-compulsive disorder (OCD) is a severe and often chronic illness, characterized by recurrent, persistent and intrusive thoughts that cause considerable distress or anxiety (obsessions) and repetitive ritualistic behaviours or mental acts that are performed excessively (compulsions). While there is considerable agreement regarding the biological substrate involved in OCD, its cause still remains a matter of debate. Available evidence from various neurobiological, genetic and treatment-response studies point toward the possibility of OCD being a heterogeneous entity, with the final common clinical stage reached through various pathways. Both genetic and environmental factors have been implicated in the causation of OCD. Although the familial nature of OCD is well established (1-4), the differing and at times modest concordance rates for monozygotic twins (5,6) suggest that only a subgroup of OCD has genetic origins, or that, the expression of the genotype may be modulated by the environmental influences. It could also be a reflection of the heterogeneity of the illness itself.

The development of obsessive compulsive (OC) symptoms following streptococcal infections reported during the last decade (7) and the frequently observed co-occurrence of OC symptoms in patients with Sydenham's chorea (SC) (8), a sequelae of rheumatic fever, which is thought to have an autoimmune basis following group A â haemolytic streptococcal (GABHS) infections (9, 10), has raised the possibility of a probable infectious &/ or immunlogical basis at least for certain types of OCD. Subsequently, evidence

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has accumulated from various sources implicating immunological processes in OCD. In this review, an attempt is made to summarize, the currently available evidence that suggest a role for immunological processes in the aetiology of OCD.

Post-infectious and/or Autoimmune Hypothesis for OCD

The idea of neuropsychiatric symptoms being post-infectious in aetiology is not new and dates back to case reports published in 1929 (11). Subsequently, a number of case reports and studies provided further support regarding the possible relationship between tics and infection and/ or immunological alteration (12-19). Since these studies, a large body of evidence has accumulated regarding the occurrence of various neuropsychiatric symptoms and conditions, particularly tics or TS following streptococcal infections (20). Evidence suggesting an autoimmune basis for tics/ TS has been important with regard to understanding the pathogenesis of OCD because of the frequent comorbidity of the two conditions as well as shared biological substrate (21).

While evidence has been accumulating regarding the possibility of tics being postinfectious in aetiology, a parallel line of evidence has also been accumulating regarding the occurrence of psychological symptoms especially OC symptoms in SC (22-25). Although, neurologic symptoms are typically the most prominent in SC, psychiatric symptoms are also well recognized. The relationship between OCD and SC also became apparent from further clinical observations that, more than 80 % of children with SC show obsessions and compulsions, both before, and concomitantly with, choreic movements (8, 26-29) and that one-third of OCD children present choreiform movements (30).

The postinfectious and autoimmune aetiology of SC was already well elucidated (9, 10) as well as involvement of the basal ganglia (BG) (31-34). In the case of SC and related disorders, a protein on the surface of Streptococcal bacteria, the M protein, was suggested as the antigenic target for the autoimmune response (35). The body of emerging literature regarding the co-occurrence of OCD and SC and tics or TS, possible shared involvement of basal ganglia in all these disorders and the elucidation of aetiopathognesis of SC as well as some forms of tic disorders led to the hypothesis, that some forms of OCD, especially those with childhood onset, could be due to immunological alterations. This was proposed first by Swedo (8). As a result, the hypothesis has emerged that infections with GABHS might produce conditions grouped together under the title of PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci), including subtypes of pediatric OCD and tics (7, 8, 36). The diagnostic criteria for this condition are available in Leonhard & Swedo (37). Validity of this diagnostic entity as well as its merits will not be discussed in this review, which will be limited to reviewing the evidence regarding the immunological basis of OCD.

Evidence for an Autoimmune Aetiology in OCD

Before an attempt to consider questions about an autoimmune aetiology in certain types of OCD and their possible relation to streptococcal infections, it is important to look at the defining criteria for autoimmune diseases (38). They include direct evidence of transfer of pathogenic antibody or pathogenic T cells; indirect evidence based on reproduction of the autoimmune disease in experimental animals; and circumstantial evidence from clinical clues. It is worth noting that in the case of OCD, most of the available evidence

suggesting an autoimmune aetiology are circumstantial in nature (39). The following discussion will first examine this circumstantial evidence in detail.

Are there Anti-brain Antibodies in OCD?

One of the most compelling types of circumstantial evidence for an autoimmune aetiology for a particular illness comes from demonstration of autoantibodies cross-reactive against the diseased organ in individuals suffering from the disease. In the case of OCD, especially in light of evidence implicating dysfunction in the cortico-striato-pallido-thalamo-cortical circuits as pathogenetic in OCD (40), it is intuitive to hypothesize that any pathogenic autoantibodies would have to be directed against components of that circuit. Very few studies have specifically investigated the presence of anti-brain antibodies in OCD patients. Most studies have either included TS and/ or tic disorder patients with comorbid OC symptoms or OCD or those satisfying the diagnostic criteria for PANDAS. In one of the earliest reports of antineuronal antibodies in OCD, Kiessling et al (17) found that sera from OCD patients showed antibodies directed against caudate, putamen or both, at a rate significantly higher than that of clinical controls. However, when Black et al (41) investigated the presence of neuron-specific, organ-specific and non-organ-specific autoantibodies in patients with OCD they found no humoral evidence of autoimmunity involving the above types of antibodies. Two other studies also found no evidence of antineuronal antibodies in individuals with OCD (42, 43). Another study attempted to establish whether anti-brain antibodies present in the sera of PANDAS patients as demonstrated in various studies represented spurious cross-reactivity with streptococcal antigens or were of pathogenic significance. Pavone et al (44) compared the presence of anti-brain antibodies in a group of PANDAS patients meeting

NIMH diagnostic criteria with a group of patients with documented GABHS infection but without neuropsychiatric symptoms and found evidence of anti-BG staining in 64% (14/22) of the PANDAS group as opposed to 9% (2/22) of the GABHS control group. They concluded that the PANDAS group and GABHS infections without neuropsychiatric disturbances differed significantly ($p<0.001$) with respect to presence of antineuronal antibodies. In a recent well-designed study, Dale et al (45) also investigated the presence of anti-brain antibodies in 50 children with OCD compared with a large number of paediatric control patients [autoimmune disorders (n=50), neurological disorders (n=100) and streptococcal infections (n=40)]. Using ELISA, they found that the mean anti-BG antibody binding was elevated in the patient group as compared to all control groups (p?0.0005 in all comparisons), while with Western blotting, they found positive antibody binding in 42% of the patient group compared with 2- 10% of control groups (p?0.001 in all comparisons). In this study, there was antibody binding to discrete BG antigens of molecular weight 40, 45 and 60 kilodalton (kDa). Significantly, other studies from the same group have previously found antibodies to a conserved group of neuronal antigens of molecular weights 40, 45 & 60 kDa, in two cohorts with SC and post-streptococcal parkinsonism similar to that found in the OCD cohort (46-48). They have also established that the 40, 45 and 60 kDa bands observed in western blotting experiments were brain-specific (48). However, another recent study (49) failed to find evidence of difference between PANDAS (n=48), TS (n=46) and age-matched control (n=43) groups with regard to presence of autoantibodies against a wide variety of epitopes, including human caudate, putamen, prefrontal cortex as well as commercially available á- and ã-enolase, aldolase C and pyruvate kinase M1, using both ELISA and western blotting technique. Morer et al (50) also did not

find any evidence of anti-BG antibodies using immunohistochemistry in sera from 32 prepubertal-onset OCD patients, 21 patients with TS and 19 healthy children. Using immunoblotting, however they were able to demonstrate antibodies binding to human putamen homogenate in 7 patients.

Although accumulating evidence has implicated autoimmunity in the causation of OCD (51), it has been unclear whether these antibodies can actually cross the blood brain barrier to bind to epitopes in basal ganglia regions and whether they are causally related to OCD, particularly in light of conflicting and negative findings of serum antibodies in OCD-related diseases (41-43, 49). In one of the first studies using CSF as well as sera from OCD patients, our group has been able to address this question partially by demonstrating significantly increased CSF autoantibody binding to antigenic proteins with molecular weights of 97 kDa, 43kDa and between 6.5 and 3 kDa in BG in a fairly large drug-naïve sample of OCD patients (n=23) compared to psychiatrically normal controls (n=23) (52). Although there were antibodies that cross-reacted to BG in the sera of patients, they did not differentiate between the patients and controls. CSF antibodies in absence of serum antibodies in our sample, might indicate intrathecal synthesis or could be a function of dilution effect. Absence of any effect of tic-disorder comorbidity (n=3) in our sample, possibly because of the small numbers involved, implicates autoimmunity even in non-tic related OCD.

Though, there are some discrepancies with regard to presence of anti-brain antibodies in the sera of patients with OC symptoms as reviewed in this section, they are likely as there are no accepted standardized methodology for assessing anti-BG antibodies (53). Different centres have differed with regard

to substrates of brain tissue utilized, ranging from immortalized neuronal cell lines to animal and human brains, as well as their preparation. Differing sensitivities of techniques like immunofluorescence, ELISA and western blotting as well different dilutions of sera used in determining presence of antibodies across the studies could also account for the discrepant findings. However, overall they appear to suggest the presence of anti-brain antibodies in OCD, particularly when considered together with the results from our group demonstrating CSF anti-brain antibodies in OCD patients, which though would need independent confirmation.

Do Infections Trigger OCD?

While evidence reviewed above suggest possible link between anti-brain antibodies and OCD, another line of circumstantial evidence has also emerged that suggest that infections act as the trigger for the autoimmune process that leads on to production of anti-brain antibodies in OCD. Large numbers of case reports and case series point towards the link between clinical and serological evidence of Streptococcal infections and acute onset of exacerbations of OCD (7, 8, 16, 27, 54-56). In one of the largest case series, Swedo et al (7) from NIMH, USA reported of 50 cases satisfying criteria for PANDAS. The children had an acute and dramatic onset of symptoms, typically triggered by GABHS infections at a very early age alongwith a relapsing-remitting symptom pattern with significant psychiatric comorbidity accompanying the exacerbations. Symptom onset was triggered by GABHS infection for 22 (44%) of the children and by pharyngitis (no throat culture obtained) for 14 (28%) others. In another study, authors (57) identified 12 patients with OC symptoms among all children who presented with a sudden onset of neuropsychiatric symptoms (such as OCD, tic disorder, or ADHD)

over a 3-year period and found the neuropsychiatric symptoms responded rapidly to antibiotic treatment, suggesting possible infectious aetiology. Two of these children also had high anti-deoxyribonuclease B titres. Subsequently, Murphy et al (58) compared the course of neuropsychiatric illness and fluctuations in GABHS titres and found that streptococcal titres correlated positively with changes in OC symptom severity ratings. Using population-based data from a large cohort (n>550,000) of individuals privately insured with a health maintenance organisation, Mell et al (59) have recently shown that recent GABHS infections were associated with an increased risk of tic disorders and OCD. However, these results have not been confirmed by Luo et al (60), who found that the association between symptom exacerbations (0.56 exacerbations per patient per year) and new GABHS infections among an unselected group of patients (0.42 infections per subject per year) with TS and/or OCD was no greater than controls (0.28 infections per subject per year) than expected on the basis of chance.

Further, indirect support regarding the possible link between OCD and streptococcal infections has come from demonstration of increased expression in OCD patients, of a peripheral lymphocyte marker, D 8/17 which has expanded expression in patients with Rheumatic fever, tic disorder, PANDAS, autism, and anorexia nervosa with a high sensitivity and specificity in comparison to controls (42, 61-66). Although initial studies suggested that increased D8/17 B cell expression could serve as a peripheral susceptibility marker for OCD associated with streptococcal infections as well as certain movement disorders, more recent studies utilizing more sophisticated methods have failed to replicate earlier findings(50, 67, 68), possibly reflecting instability of the antibody (51).

While majority of studies have investigated the link between streptococcal infections & OCD, there have been some notable exceptions. Studies from India have investigated the role of viral CNS infections in the causation of OCD. Khanna et al (69) studied IgG viral antibodies in the sera of OCD patients and controls and found that there was a significantly higher titre for HSV1 and Mumps viruses in the sera of OCD patients compared to controls. In the same group of patients, the authors also analyzed CSF viral antibodies and found an increase in titres in CSF IgG antibodies to HSV1 with evidence for intrathecal origin for the HSV1 specific IgG on the basis of sera: CSF ratios. In a follow up study (70), investigating the issue of viral infections and OCD, the authors traced six surviving patients out of 11 who received a definite diagnosis of Herpes simplex encephalitis during the period 1980-1992. Out of five patients who could be interviewed, two were found to have subclinical OCD. They also reported of two other patients with Herpes simplex encephalitis who had developed OCD and postulated that subjects who have had Herpes simplex encephalitis were at risk to develop OC symptoms probably due to either a shared neuroanatomical substrate in the frontal and temporal regions or due to shared neuropsychological deficits involving visual and verbal memory. Studies from other centres have also suggested link between Borna disease virus (71-73) and Mycoplasma Pneumoniae (74, 75) infections and OCD.

Though a relationship between an infectious agent and a disorder does not prove causality, it is often the first indication suggesting an aetiologic relationship (76, 77). Because streptococcal infections are widespread, it is worth remembering that an association with OCD and/or OC symptoms can also occur by chance. Also, correlating timing and certainty of a streptococcal

infection with onset of OCD symptoms is often difficult. Though prospective studies employing serial streptococcal titre estimations rather than cross-sectional analyses would possibly help clarifying this association with further certainty, the available data tends to suggest a link between GABHS infections and OCD. More interestingly, evidence reviewed here tends to suggest that the role of infections may not be limited to streptococci alone. As viruses are also well-known to cause autoimmune diseases (78), more investigations examining this link are warranted.

Are There Other Immunological Alterations in OCD?

While all these studies point toward specific immunological dysfunction related to exposure to infection in OCD patients, there have been other evidences of immune dysfunction of a more nonspecific nature in OCD patients. Roy et al (79) first showed that OCD patients had elevated serum antibodies against Somatostatin release inhibiting factor-14 (SRIF-14) and prodynorphin 209-240 which they thought was consistent with epitope-specific immunity, and speculated that autoantibodies may interfere with peptide action and lead to OCD through alteration in opioid peptides. However, though another study reported reduced serum -endorphin in OCD (80), other studies did not find any correlation between obsessive symptoms and measurements of CSF dynorphin (81, 82). In the earliest study from the Indian subcontinent examining immune dysfunction in OCD, Khanna et al (83) showed that higher levels of immunoglobulins especially IgG were found in drug-free OCD patients compared to healthy controls. As immunoglobulin levels continued to remain stable even after clinical improvement with 8 weeks of pharmacotherapy, they hypothesized that immune dysfunction was a trait rather than a state marker of OCD and may indicate a predisposition of OCD

patients to infections of the CNS. Elsewhere, though Weizman et al (84) did not find any alteration in the in vitro production of cytokines (Interleukin-1, Interleukin-2 and Interleukin-3-LA) by peripheral blood mononuclear cells in drug-free OCD patients compared to controls as well as no effect with 8 weeks of drug-treatment, Brambilla et al (85) showed that plasma Interleukin-1 and Tumor Necrosis factor-á levels were significantly lower in OCD patients compared to healthy controls. Mittleman et al (86) showed that there was a relative skewing in favour of type 1 cytokines (Interleukin-2, Tumor necrosis factor-, Interferon-ã), in the CSF of paediatric OCD patients, while there was a relative lack of type 2 cytokines, with absence of detectable Interleukin-4 and Interleukin-10. Later on, Marazziti et al (87) showed that patients with adult OCD had increased CD8+ i.e suppressor T lymphocytes and decreased CD4+ i.e. helper T lymphocytes compared to healthy control subjects. However, Maes et al (88) failed to find any significant differences between OCD patients and healthy controls with regard to a host of immune markers including interleukin-1 beta, interleukin-6, soluble interleukin-6 receptor, soluble interleukin 2 receptor, transferrin receptor and baseline cortisol and later Carpenter et al (89) also failed to find any evidence for alteration in interleukin-6 level in the CSF of OCD patients compared to healthy control subjects. Ravindran et al (90) found elevated circulating natural killer cells in male OCD patients compared to controls, which did not normalize with treatment. In another study, Denys et al (91) also found that OCD patients had a significant decrease in production of TNF-á ($p<0.0001$) and NK activity ($p=0.002$) in comparison with controls. In a subsequent prospective longitudinal study, Leckman et al (92) found interleukin-12 & TNF- á were elevated at baseline with a further increase of both markers during symptom exacerbation in a mixed group of TS or childhood-onset OCD compared with age-matched controls.

Although, it appears that there are no consistent changes in interleukins, T-cells or TNF in OCD, it is likely that the discrepancies are due to methodologic differences or age-related developmental influences in certain cases (93). However, as there are well documented interactions between stimulation of the peripheral immune system and central cytokine expression (94), peripheral changes observed in OCD can actually cause CNS effects. Importantly, TNF-á has been implicated in leukocyte recruitment across the blood-brain in vivo, perhaps opening the door for both B and other immune cells to enter the CNS (95).

Are Immunosuppressive Agents and Antibiotics Effective in OCD?

Another crucial component of the circumstantial evidence supporting a causal link between autoimmunity and OCD stems from studies that have investigated immunosuppressive agents and antibiotic prophylaxis in OCD. Cases have been reported where patients with OCD associated with streptococcal infections who have not responded to the conventional treatments have responded to treatments like plasmapheresis (54, 96, 97). There have also been a number of controlled trials investigating beneficial effects of such treatments systematically. Garvey et al (98) examined the beneficial effects of penicillin prophylaxis in preventing symptom exacerbations in a pilot study with a double-blind randomized balanced cross-over placebo-controlled design, in 37 children with PANDAS. They found that the number of infections did not differ between the active and placebo phases which lasted 4 months each, and there was no significant change in OC or tic symptom severity. They concluded that failure to achieve an acceptable level of streptococcal prophylaxis led to their inconclusive results. In a subsequent

study from the same group (99), the authors tried to correct the potential confounds in the first study, by addressing the issue of compliance as well as increasing the study duration to 12 months. In this double-blind, randomized parallel-design study, where 11 patients satisfying diagnostic criteria for PANDAS were treated with Penicillin prophylaxis and 12 patients satisfying similar criteria were treated with Azithromycin prophylaxis for the study duration, the authors found significant decreases in number of streptococcal infections ($p<0.01$) and exacerbations in neuropsychiatric symptoms ($p<0.01$) in the study year for both drugs compared to the baseline year prior to entry. Although, comparison of prospective data of the treatment year with retrospective data of the baseline year is a significant limitation in the design of this study, it nevertheless adds to the circumstantial evidence suggesting role of an infectious process in the aetiology of some patients with OCD, who fulfil the diagnostic criteria for PANDAS. Earlier, another study from the same group (97, 100) also added to this evidence by demonstrating that plasmapheresis or intravenous immunoglobulin (IVIG) treatment in children with severe infection-triggered exacerbations of OCD/ or tic disorders resulted in marked improvement in severity of OC and tic symptoms which were maintained in follow-up in 82% of the children. However, the small sample size in each of the treatment arms (IVIG=9; Plasma exchange=10, Placebo 10) of this study limits the interpretation of these results.

As it appears that streptococcal infections are possibly not the only triggering events and viral infections might also be involved in triggering an autoimmune process in OCD, negative or inconclusive results from studies investigating the beneficial effect of antibiotic prophylaxis in reducing the onset and/ or exacerbations of OCD/ PANDAS are only to be expected.

Is There Evidence of an Inflammatory Process Going on in the OCD circuit?

While evidence of inflammatory processes, either in the form of deposition of antigen-antibody complexes or infiltration with mononuclear cells, occurring in the OCD circuit in the brain of patients is difficult to document for obvious reasons, indirect evidence of volume changes in BG in OCD patients that responded to treatment with immunomodulation, with concomitant reduction in symptoms (96, 97), has led to the understanding that the initial volume increase might be related to an inflammatory process. Peterson et al (101) investigated the relationship of antistreptococcal antibody titres, profiles of BG volumes and diagnoses of Chronic tic disorder, OCD or ADHD, in a sample of 105 patients and 37 community controls and found that, in subjects who had ADHD, OCD, or both disorders, higher antibody titres predicted larger putamen and globus pallidus volumes on MRI.

Is it Possible to Induce OCD in Another Human Being or Animal by Transferring Pathogenic Antibody or Pathogenic T Cells from an Affected Individual?

While presence of autoantibodies in serum and CSF is highly suggestive of an auto-antibody mediated disorder, direct evidence of existence of autoimmunity requires transmissibility of the characteristic lesions of the disease to another organism, either human or animal. Several studies have attempted to confirm a causal effect of antineuronal antibodies by passive transfer of patient IgG to animals (102-105). Hallett et al (102) found that dilute serum (1:6) from only TS patients and not controls, infused into the ventral striatum of rats produced a significant increase in stereotypies as well as episodic utterances in rats. Taylor et al (103) found a significant increase in

oral stereotypies in rats receiving higher titre TS sera as compared to lower titre patient sera and control sera infused into ventrolateral striatum. However, Loiselle et al (104) did not find any significant increase in stereotypic behaviours or development of auditory abnormality in rats following microinfusion of sera from subjects with TS and PANDAS into ventral or ventrolateral striatum. In a subsequent collaborative study performed in three institutions with the same sera, there was no significant difference in stereotypic behaviours induced by sera from neuropsychiatric patients (TS, ADHD, OCD) containing either elevated or low concentrations of antineuronal antibodies (105), the finding being consistent across all individual centres as well as when analyzed as total mean values. However, in another study a subset of mice immunized and boosted with a streptococcal homogenate in Freund's adjuvant was demonstrated to exhibit motoric and behavioural disturbances in association with the presence of serum antibodies that were immunoreactive to several brain regions including globus pallidus and thalamus, consistent with the hypothesis that immune response to streptococci can result in motor and behaviour alterations (106).

Thus, it appears that the evidence that would have constituted the strongest evidence in support of an autoimmune aetiology of certain types of OCD remains inconclusive at this time.

How Can Autoantibodies or Cellular Immune System Dysfunction Lead to OCD?

Although the immune system protects human beings from microbial infections, at times, such infections can also trigger autoreactive or autoimmune responses directed against self antigens. Such responses are quite

frequent (107), but are usually low-grade and harmless (108). Hence, detection of autoimmune (autoreactive) antibodies or T cells in an individual does not invariably imply the existence of autoimmune disease. But sometimes, the autoreactive responses are sufficiently severe to be called autoaggressive and can result in autoimmune disease. Thus, although the presence of anti-brain antibodies and altered T-cell and cytokine response in OCD is suggestive of involvement of an autoimmune process in the aetiopathogenesis of OCD, there is no conclusive evidence as yet that they have pathological significance. While that might be difficult to be proven conclusively, further elucidation of the plausible pathological mechanisms by which these autoimmune responses might cause symptoms of OCD would strengthen the autoimmune hypothesis of OCD. There are at least two possible mechanisms underlying microbial infection-induced autoimmunity. One involves cross-reactivity between the microbial and host antigens because of similar epitopes or 'molecular mimicry' (10, 109) and the other requiring no such antigenic similarity.

In the case of OCD hypothesized to be caused by anti-brain antibodies triggered by GABHS infection, one of the key steps in elucidating the plausible pathological mechanism involves identification of the autoantigens that share epitopes with GABHS. Kirvan et al (110, 111) have demonstrated that majority of SC and PANDAS sera contain antibodies which react with lysoganglioside Gìý and induce CaM kinase II activation in neuronal cells. As CaM kinase II is highly concentrated in the brain with functions in neurotransmission and neuronal excitability (112) and colocalized with glutamate receptors, which are implicated in the pathophysiology of OCD (113, 114), this suggests a plausible mechanism by which anti-brain antibodies

can trigger OC symptoms. In another recent study, Dale et al (115) have defined the antigens identified by their group as targets of autoantibodies in a wide-range of post-streptococcal neuropsychiatric syndromes including OCD in previous studies (46-48). The autoantigens were found to be glycolytic enzymes expressed on the neuronal cell surface, three being neuronal specific (Neuron-specific enolase, aldolase C, Pyruvate kinase M1) and the other being Non-neuronal enolase. M1 subtype of the glycolytic enzyme Pyruvate kinase was also independently identified as an antigenic target in disorders including OCD by another group of researchers (116). Dale et al (115) speculated that antibodies to these neuronal glycolytic enzymes may induce apoptosis due to local energy failure at the cell surface. They also hypothesized that as BG, especially some populations of striatal neurons (such as GABAergic medium spiny neurons) are vulnerable to metabolic stress and a variety of energy-dependent CNS diseases (117), autoantibodies directed against these enzymes could result in corticostriatal excitation by causing selective impairment of GABAergic neurons. Interestingly, as OCD is thought to involve hyperactivity of the cortico-striato-pallido-thalamic pathways, corticostriatal excitation caused by antibodies directed against neuronal glycolytic enzymes located on striatal medium spiny neurons could potentially lead to OC symptoms.

While the above account suggests possible ways how anti-brain antibodies could lead to OC symptoms, there are also interesting CNS effects of cellular immune system activation that are potentially significant for the pathogenesis of OCD. For example, TNF-á constitutively produced by glia has been shown to influence synaptic strength at excitatory synapses via rapid effects on trafficking of AMPA (á-amino-3-hydroxy-5-methyl-4-isozolepropionic acid)

receptors (118). Hence, Leckman et al (92) speculated that if TNF- á levels were increased at excitatory glutamatergic synapses in the striatum, subthalamic nucleus or globus pallidus, it could alter neuronal activity including the release of dopamine after local activation of AMPA receptors, possibly leading to TS or OC symptoms. Considered together with the report of elevated levels of TNF (ligand) superfamily, member 10, in the putamen of 3 TS patients on microarray (119), evidence of altered cytokine system in OCD patients as reviewed earlier suggests a possible way through which OC symptoms could be produced by these alterations.

Conclusions

Thus despite some discrepancies, possibly related to methodological differences, there is a reasonable body of data to suggest that there is immunological alteration in the form of either anti-brain antibodies or activation of the cytokine system in OCD. However, the issue of whether this immune activation is also present in the CSF of patients needs further replication. There is also a fairly strong suggestion that this immune activation is linked to an infective process, not necessarily limited to streptococcal infections. It is also likely that this immune activation is of pathogenic significance in OCD, though this would need more definitive evidence of positive studies showing transmissibility of the disease from human to animal models. Evidence also suggests that the antigenic targets are located, but possibly not limited to the BG and the corresponding autoimmune activation (antibody or T-cell mediated) directed against these targets could cause OC symptoms by altering excitatory neurotransmission through either involvement in neuronal cell signalling or selective impairment of certain neuronal populations. However, further studies are needed replicating

evidence of anti-brain antibodies or T-cell activation, not just in sera but more importantly, in the CSF of patients, followed by identification of the antigenic targets and then specifically exploring the issue of transmissibility of antibodies isolated from CSF to animals. It is also likely that genetic diathesis may interact with environmental triggers like infections in OCD, and studies exploring this link are warranted. One could speculate that, while autoimmune activation directed against the brain can occur in a number of individuals, such activation will cause OC symptoms only in individuals who are genetically vulnerable. Thus, any studies that explore the issue of transmissibility to animals without taking into the account the genetic vulnerability issue are unlikely to yield conclusive results. Taken together, such studies would provide conclusive evidence regarding involvement of autoimmune processes in the pathophysiology of OCD.

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Chapter 6

Childhood Obsessive-Compulsive Disorder: What is Unique About It?

Daniel A. Geller

Introduction

Obsessive-Compulsive Disorder (OCD) is one of the most prevalent psychiatric disorders affecting children and adolescents and is projected to be among the ten leading causes of global disability by the World Health Organization (1). Although categorized among the anxiety disorders in the DSM IV-TR (2), a variety of affects may drive the symptoms of OCD, which are frequently hidden or poorly articulated, especially in younger children. Therefore, pediatric OCD is under diagnosed and under treated (3). In the last decade our knowledge of pediatric OCD has increased with

large scale genetic and family studies

the emergence of research on immune-based neuropsychiatric causes (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus - PANDAS)

elaboration of phenotypic dimensions; understanding of comorbid disorders and their moderating effects on treatment response and outcome

publication of randomized controlled trials of selective serotonin re-uptake inhibitors (SSRIs) in children

concern and scrutiny regarding safety of these SSRIs in children; the first large scale randomized controlled trials of cognitive behavioral

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therapy (CBT)

new approaches in behavior therapy including intensive in- and outpatient treatment, family-based treatment, group therapy and behavioral intervention for very young children with OCD.

These research advances in children and adolescents with OCD suggest that childhood-onset OCD is a developmental subtype of OCD with unique correlates. The attempt here is to highlight clinical phenomenology with attention to symptoms, insight, neuropsychological findings, comorbid psychopathology and functional impairment as well as familial and genetic patterns of transmission and immune-mediated pathophysiology of pediatric OCD.

Epidemiology

The high prevalence of OCD in children was not generally recognized until the first epidemiological study just over 20 years ago (4). Early epidemiological studies were all conducted on adolescent populations and most used school surveys for sample ascertainment. Prevalence rates of pediatric OCD are around 1%-2% in the USA and elsewhere (5-9). In the more recent British Child Mental Health Survey of over 10,000 five to fifteen year olds, the point prevalence was 0.25% and almost 90% of cases identified had been undetected and untreated. In this study, lower socioeconomic and intelligence quotients were associated with OCD in youth (3). There are two peaks of incidence for OCD across the life span, one occurring in pre-adolescent children (10) and a later peak in early adult life (11). If all pediatric cases of OCD persisted in adulthood, we would expect an increasing cumulative prevalence of OCD across the life span as more cases (new incidence) are

added to the population. However, the anticipated cumulative increase in prevalence does not occur because of the variable outcome of childhood-onset OCD, with a substantial number becoming subclinical over time (12). The finding of a bimodal incidence of OCD raises important questions regarding etiology and underlying pathophysiology of the juvenile subtype in the same way that type I and type II diabetes have the same syndromatic clinical features but differ in other critical ways.

Clinical Features

Despite apparent continuity in the phenotypic presentation of children and adults, issues such as limited insight and evolution of symptom profiles that follow developmental themes over time differentiate children from adults with OCD (13-16). In addition, children with OCD frequently display compulsions without well-defined obsessions, and symptoms other than typical washing or checking rituals (e.g., blinking and breathing rituals) (17). One review on pediatric OCD (10), indicated that although the majority of children exhibit both multiple obsessions and compulsions (mean number over lifetime was 4.0 and 4.8 respectively (14), compulsions only without obsessions were more common in children than adolescents. Often children's obsessions centered upon fear of a catastrophic family event (e.g. death of a parent). These studies also reported that although OCD symptoms tended to wax and wane, they persisted in the majority of children but frequently changed over time so that the presenting symptom constellation was not maintained (17). In many studies, parents are noted to be intimately involved in their child's rituals, especially in reassurance seeking, a form of 'verbal checking'. In another study that examined effects of age on symptom constellation (13) found that religious and sexual obsessions were selectively over represented in

adolescents compared with children and adults. Only hoarding was seen more often in children than in adolescents and adults. These findings provide evidence for developmental influences in the phenotypic expression of the disorder and may be understood in the context of conflict and anxiety negotiating expected stages of attachment, autonomy, and sexual and moral development. As a corollary, rates of separation anxiety disorder appear inversely proportional to age and as high as 56% in childhood subjects (13).

Factor or cluster analytic methods take into account the broad phenotypic heterogeneity of OCD by identifying consistent symptom 'dimensions' in OCD rather than a categorical (present/not present) diagnostic approach. Stewart et al (18) conducted an exploratory principal components analysis of obsessive-compulsive (OC) symptoms in children and adolescents with OCD to identify dimensional phenotypes. A four-factor solution emerged explaining 60% of symptom variance characterized by:

symmetry/ ordering/ repeating/ checking
contamination/ cleaning/ aggressive/ somatic
hoarding
sexual/ religious symptoms

This solution also suggested fairly consistent covariation of OCD symptoms across the lifespan.

The dimensional approach to phenotyping OCD provides a new research method that may yield important biological signals in genetic, translational and treatment studies where more traditional DSM IV/ICD 10 approaches do not.

Unlike adult OCD, pediatric OCD is characterized by male predominance

(19). In a review of studies reporting on 419 childhood OCD patients, all but one study reported a male predominance with an average of a 3:2 male to female (10). Two reports found that boys had an earlier age of onset of OCD than girls. Adult gender patterns appear in late adolescence. The mean age of onset of pediatric OCD ranged from 7.5 to 12.5 years (mean: 10.3 years, SD 2.5 years) and the mean age at ascertainment ranged from 12 to 15.2 years (mean: 13.2 years) (10). In other words, age at assessment generally lagged 2.5 years after age at onset, a finding of considerable clinical importance and consistent with the secretive nature of the disorder.

Neuropsychological Findings

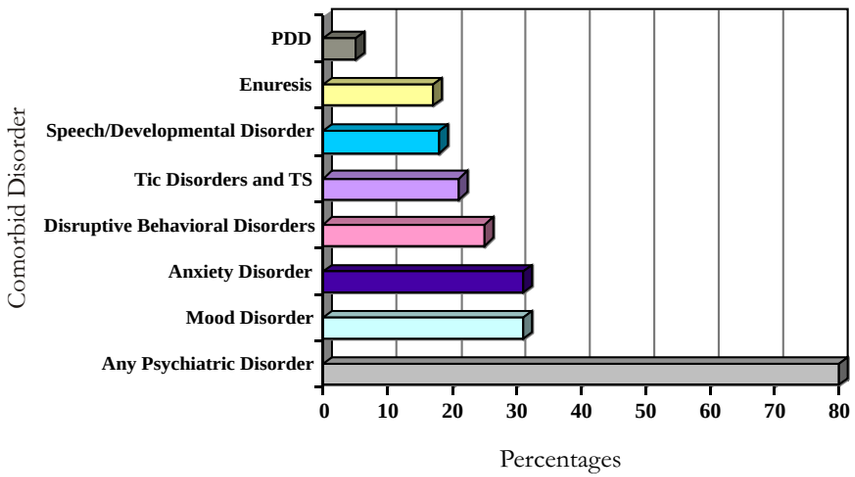
Although not part of the core diagnostic symptoms, interest in the neuropsychological 'endophenotype' of children with OCD has grown over the last several years out of clinical and anecdotal experience that many children have academic difficulties that are not wholly explained by their primary disorder. Given the potential involvement of frontal-striatal systems in OCD, several aspects of neuropsychological performance have been especially relevant to its study, especially measures of visuospatial integration, short-term memory, attention and executive functions. Few studies have examined neuropsychological processes among children with the disorder (20). A handful of early studies of children with OCD yielded inconsistent results with deficits in executive functioning, visuospatial performance and attention implicating basal ganglia dysfunction (21, 22), and deficits in Verbal IQ, achievement, and executive functioning (23), while other studies failed to find significant neuropsychological deficits among youth with OCD (8, 24, 26). In a related line of research, Rosenberg and colleagues examined cognitive functions associated with the prefrontal cortex, using an oculomotor

paradigm, and found that pediatric OCD subjects demonstrated higher response suppression failures than controls that were correlated with impairments on measures of frontostriatal functioning (27, 28). More recently, Andres et al (29) examined the neuropsychological performance in children and adolescents with OCD and showed impairment in visual memory, visual organization and velocity (processing speed). Although not yet well characterized, deficits in visual spatial performance and processing speed appear common and may underlie academic dysfunction in affected children.

Comorbidity

OCD in youth is usually accompanied by other psychopathology that may complicate the assessment and treatment of affected children. Even cases derived from epidemiological studies that avoid the referral bias inherent in many clinical studies, demonstrate rates of comorbid psychiatric diagnoses in over 50% of children with OCD (8, 30). Furthermore, while OCD symptoms in children are usually chronic, this comorbid psychopathology often shows a

Figure 1. Comorbid Disorders in Pediatric OCD



distinct chronology so that assessment and treatment approaches must evolve with time. A review of clinical studies consistently reported not only high rates of tic disorders, but also mood, anxiety, ADHD, disruptive behavior, specific developmental disorders and enuresis in youth with OCD (10) (Figure 1).

In addition to an increased association with tics and Tourette's syndrome (31, 32), many investigators have reported higher frequency of learning disabilities (LD) (15) and frequent comorbidity with disruptive behavior disorders (33, 34). Irrespective of age at ascertainment, an earlier age at onset predicts increased risk for ADHD and other anxiety disorders. In contrast, mood and psychotic disorders are associated with increasing chronological age and are more prevalent in adolescent subjects. Tourette's syndrome is associated with both age at onset (earlier onset is more likely to be associated with comorbid TS) and chronological age (adolescents usually show remission of tics).

Whether comorbid psychiatric symptoms in youth are artifacts of, or 'secondary' to OCD or whether they reflect true comorbid states may be determined by family and genetic studies that examine the prevalence and segregation of comorbid diagnoses in relatives of children ascertained with OCD as the primary disorder. Whether comorbid disorders modify the expression or outcome of pediatric OCD when they occur is uncertain. There is some evidence that this is so in the case of TS, where specific symptoms (touching, tapping, repeating) appear more common than in non tic-disordered patients (35). By contrast, the OCD phenotype appears independent of the presence or absence of ADHD in either symptoms, patterns of comorbid disorders, or OCD-specific functional impairment (36). In any case, the presence (or absence) of comorbid psychopathology is

important for clinicians to identify, not only because they may require treatment in their own right, but because of their relevance for course and outcome as well as treatment response.

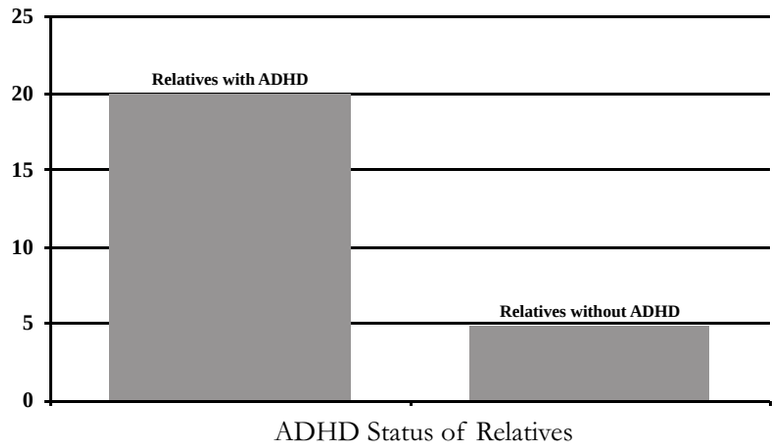
Genetic Factors

The contribution of genetic factors to the development of OCD has been explored in twin, family genetic and segregation analyses studies (32, 37-41). While family studies consistently demonstrate that OCD is familial (32, 40, 42-45), the morbid risk of OCD in first-degree relatives appears to be much greater for index cases with a childhood onset. For example, in their multi-site family study of OCD, Nestadt et al (37) found a risk for OCD of around 12% in first degree relatives while relatives of pediatric OCD probands have shown age-corrected morbid risks from 24-26% in more recent studies (46-49) with the last two studies including control samples. These findings suggest a greater genetic loading in pediatric onset OCD. A further substantial proportion of relatives (5-15%) are affected with subthreshold OC symptoms that speak of genetic influences (32, 37) but may also be relevant to family functioning.

In a familial risk analysis examining the genetic association between OCD and ADHD in children, Geller et al (50) found that (Figure 2):

1) relatives of children with OCD with and without ADHD had similar and significantly higher rates of OCD than did relatives of non-OCD comparison children;
2) the risk for ADHD was elevated only among relatives of OCD+ADHD probands;
3) there was evidence of co-segregation between OCD and ADHD in affected relatives; and

Figure 2. Rate of Obsessive-Compulsive Disorder (OCD) among relatives with and without Attention-Deficit/Hyperactivity Disorder (ADHD) in families of probands with Pediatric OCD.



4) there was no evidence of nonrandom mating between parents affected with OCD and ADHD.

These findings are most consistent with the hypothesis that, in children, OCD that is comorbid with ADHD represents a distinct familial subtype. Considerable indirect support for a finding that some forms of ADHD and OCD are etiologically (and genetically) related can be found in the literature using Tourette's syndrome (TS) as a conceptual link between these two disorders. For example, many investigators have reported a higher than expected frequency of OCD among TS patients (51-55). Gilles de la Tourette himself anecdotally reported OCD symptoms in one of his original patients. In addition, very high comorbidity between ADHD and TS has been reported in almost every study of pediatric patients with TS (56-58). Furthermore, twin studies implicate genetic factors as important for the expression of all three

disorders (59-65). Family studies have also demonstrated that TS and OCD as well as TS and ADHD often co-occur and co-segregate within families (32, 38, 47, 48, 54, 66). Given the frequent comorbidity that has been observed between TS, OCD and ADHD, it is also plausible that there could be some common susceptibility genes for some components of these three conditions in which several overlapping neurologically mediated behaviors could occur.

If OCD with comorbid ADHD represents a distinct familial subtype, then genetic studies could be informed by evidence of co-segregation in affected relatives. From a clinical perspective, children and their relatives affected with OCD plus comorbid ADHD may have differing treatment response and outcome compared with their non-comorbid counterparts and manifest more OCD spectrum disorders that involve greater degrees of impulsivity such as pathological gambling, trichotillomania or binge eating disorders (67).

Because early onset OCD is a more familial form of the disorder, several researchers have used families ascertained from childhood-onset OCD cases to look for association at common polymorphisms in several serotonin transmitter system genes but found only nominal association in two serotonin genes previously reported to have shown association in single studies. Although no single study showed replication, a pooled analysis of 5 replication studies found the marker SLC6A4HTTLPR, a functional length polymorphism found in the promoter region of SLC6A4 that encodes for the serotonin transporter protein, to show significant association (68). More recently interest in glutamatergic mechanisms in the pathophysiology of OCD has led to study of the glutamate transporter gene *SLC1A1*(69-72).

Non-Genetic Factors

While the above studies emphasize genetic factors they also point clearly to major effects of non-genetic influences in the expression of OCD. In a cross-cultural sample of 4246 twin pairs, Hudziak et al (73) used structural equation modeling to examine the influence of both genetic (45%-58%) and unique environmental (42%-55%) factors and concluded that both factors are about equally important. In fact, many if not most cases of OCD arise without a positive family history of the disorder-so called 'sporadic' cases. It is generally assumed that sporadic cases have less genetic loading than familial cases. Information regarding environmental triggers of the disorder may be especially relevant for the sporadic form since the OCD cannot be explained by the presence of an affected relative. To date studies have focused on perinatal (intra-uterine, birth and post-natal) experiences of affected children and immune mediated neuropsychiatric models of illness. The intrauterine environment also includes exposure to potential teratogens such as alcohol and tobacco.

Lensi et al (74) collected perinatal histories from 263 patients as part of a study on gender differences in OCD and found a higher rate of perinatal trauma (defined by dystocic delivery, use of forceps, breech presentation or prolonged hypoxia) in males with an earlier onset of OCD. In another study of 60 pediatric probands with Tourette's syndrome (TS), Santangelo et al (75) found that TS probands with comorbid OCD (n=33) were almost 8 times as likely to have been delivered by forceps than those without OCD and 5 times more likely to have been regularly exposed to coffee, cigarettes and alcohol in utero. A similar study by Mathews et al (76) also identified drug exposure in utero as a significant predictor of increased tic severity and comorbid OCD status in a sample of 180 probands (ages 3 to 59) with TS.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS)

Since its original description (77), perhaps no issue in pediatric OCD remains as controversial as the debate around PANDAS. The central hypothesis of PANDAS derives from observations of neurobehavioral disturbance accompanying Sydenham's chorea, a sequela of rheumatic fever. An immune response to group A beta-hemolytic streptococcus (GABHS) infections leads to cross reactivity with and inflammation of basal ganglia with a distinct neurobehavioral syndrome that includes OCD and tics. Diagnostic criteria laid out by Swedo et al (78) (Table 1), have been used in a variety of antibiotic prophylaxis (79, 80) studies but detractors argue that GABHS is but one of many non-specific physiological stressors that can trigger an increase in tics or OCD (81). The weight of evidence at this time supports the belief that a subset of children with OCD and Tourette's syndrome can have both onset and clinical exacerbations linked to GABHS. In a 2-year prospective longitudinal case control study of children with putative PANDAS linked

Table 1: Diagnostic Criteria for PANDAS

1. Presence of obsessive-compulsive disorder and/or a tic disorder
2. Prepubertal onset between 3 and 12 years of age, or Tanner I or II
3. Episodic course (abrupt onset and/or exacerbations)
4. The symptom onset or exacerbations are temporally related to *two* (2) documented GABHS infections
5. Association with neurological abnormalities (motor hyperactivity, choreiform movements, and/or tics)

Adapted from Swedo et al (77)

OCD and TS, clinical exacerbations linked to GABHS were significantly elevated in PANDAS-identified children. However, in these children, assessment of multiple immune markers did not demonstrate any differences between PANDAS and non-PANDAS cases (personal communication*). Much is yet to be understood about the immunology of streptococcus and its role in infection-triggered neuropsychiatric symptoms.

The Role of the Family in Pediatric OCD

Parents are often intimately involved in their children's OC symptoms and may unwittingly reinforce compulsive behaviors by providing verbal reassurance or other 'assistance' to children (for example, handling objects that children avoid such as opening doors, laundering 'contaminated' clothes and linens excessively, even wiping children on the toilet who will not do it themselves). Since OCD, and an anxiety diathesis in general, are highly familial, disentangling parental psychopathology from disturbed family functioning associated with the child's OCD is critical, especially in the younger patient whose parents control many contingencies of their daily behavior and who are therefore dependent on parents for may activities of daily living. Increasingly, the central role of family (both for maintenance of pathology as well as therapeutic agents) in children affected with OCD has been recognized and is reflected in both broader assessment that evaluates family function, and newer models of treatment intervention.

Course and Prognosis

The long-term prognosis for pediatric OCD is better than originally conceived (12, 82, 83) and better than described for adults. Many children will

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remit entirely or become clinically subthreshold over time. Adverse prognostic factors include very early age at onset, concurrent psychiatric diagnoses, poor initial treatment response, long duration of illness and a positive first-degree family history of OCD. In a review of outcome studies, Stewart et al (12) applied meta-analysis regression to evaluate predictors and persistence of OCD. Sixteen study samples reported in 22 studies with a total of 521 children with OCD and follow-up periods ranging from 1-15.6 years (mean 5.7 years) showed pooled mean persistence rates of 41% for full OCD and 60% for full or subthreshold OCD. Earlier age of OCD onset, increased duration of OCD and in-patient treatment predicted greater persistence. Comorbid psychiatric illness and poor initial treatment response were poor prognostic factors. Concurrent psychopathology including multiple anxiety disorders, major mood disturbance and disruptive behavioral disorders may reduce acceptance of or compliance with treatment and the consideration of comorbid disorders in youth with OCD is not an academic matter. The influence of psychiatric comorbidity on response and relapse rates in children and adolescents treated with paroxetine for OCD (84) showed that while the response rate to paroxetine in the overall treated sample was high (71%), the response rates in patients with comorbid ADHD, tic disorder, or ODD (56%, 53%, and 39%, respectively) were significantly less than in patients with OCD only (75%). Further, comorbidity was associated with a greater rate of relapse in the total patient population (46% for $\geq$1 comorbid disorder ($p=0.04$) and 56% for $\geq$2 comorbid disorders ($p<0.05$) vs. 32% for no comorbidity). More recent work has confirmed these findings. March et al (85) conducted a post hoc analysis of data from the NIMH-funded Pediatric OCD Treatment Study (POTS) (86) comparative treatment trial to find the extent to which the presence of a comorbid tic disorder influenced symptom reduction on the Children's Yale-

Brown Obsessive Compulsive Scale (CY-BOCS) predicted score after 12 weeks of treatment. Those children with a comorbid tic disorder failed to respond to sertraline and did not separate statistically from placebo-treated patients while response in youth with OCD but without tics replicated previously published intent-to-treat outcomes. In children with tics, sertraline was only helpful when combined with CBT while CBT alone without medications remained effective. The presence of disruptive behavior disorders in particular may represent a therapeutic challenge for clinicians, especially cognitive behavioral clinicians. Storch et al (87) examined the impact of psychiatric comorbidity on CBT response in children and adolescents with OCD treated systematically with standard weekly or intensive family-based CBT. Those children with one or more comorbid diagnoses had lower treatment response and remission rates with CBT relative to those without a comorbid diagnosis. As in the paroxetine study, the number of comorbid conditions was negatively related to outcome. Since certain comorbid disorders may adversely impact the outcome of both CBT and medication management of pediatric OCD, assessment and treatment of other psychiatric disorders prior to and concurrent with treatment of OCD may improve final outcome.

In contrast, gender, age at assessment, length of follow-up and year of publication were not reported as predictors of remission or persistence. Conclusions regarding the predictive importance of early treatment and family psychiatric history cannot yet be drawn from the extant literature. Psychosocial function is frequently compromised. In five of the studies reviewed, subjects were less likely to live with a partner and between 52-100% were unmarried. In one study 30% were still living with their parents as adults

and in another there was a marked pattern of hiding symptoms from family. These studies report high levels of social/peer problems (55-100%), isolation, unemployment (45%) and difficulties sustaining a job (20%).

Conclusions and Research Directions

There is considerable support for the notion that, while diagnosed using identical DSM IV criteria, OCD that affects children is distinct in important ways from the disorder seen in adults.

1. OCD is common in children and adolescents and is frequently under-diagnosed and under-treated due to the secretive nature of its symptoms.
2. Phenotypically, OCD in children is characterized by developmentally specific symptom profiles that reflect the conflicts of their age group.
3. Families often become enmeshed in their children's rituals.
4. Most often, OCD in children is accompanied by a distinct pattern of comorbid psychopathology that has a real impact on morbid functioning and treatment outcome.
5. Tic disorders, Tourette's syndrome and ADHD are selectively over-represented in children with OCD and are genetically linked to pediatric OCD.
6. The risk of OCD in first-degree relatives of childhood cases is markedly elevated compared with adult onset OCD.
7. Immune-mediated etiology of neuropsychiatric symptoms that include OCD and tics is unique to childhood-onset OCD
8. Outcome in childhood onset OCD is better than previously recognized and generally better that outcome in adults.

The increasing power of genome-wide association methods and of pooling data, such as made possible by the newly created OCD International Genetics Consortium can be exploited to advantage by recruiting childhood probands to increase the yield in genetic studies. Ever more powerful magnets provide a non-invasive and child-safe method for endophenotypic, translational and pharmacogenomic studies that should increase specificity of treatments to improve effect sizes and decrease adverse events. Novel therapeutic approaches employing glutamatergic, gaba-ergic and peptide neurotransmitter manipulation are likely and will be informed by genetic studies. Real challenges remain in identifying environmental triggers (in genetically susceptible children) as only prospective long-term studies of as-yet-unaffected 'at-risk' children can hope to understand the complex gene-environment interactions that underlie most cases of pediatric OCD.

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Chapter 7

Childhood Obsessive-Compulsive Disorder - A Perspective from India

Shoba Srinath and Y C Janardhan Reddy

Introduction

Obsessive-compulsive disorder (OCD) was rarely diagnosed in children and adolescents until recently. It is now well-known that a large number of youngsters are silent sufferers of this potentially treatable disorder. The availability of effective treatments for this disorder has impacted the outcome. This chapter focuses on the studies done at the National Institute of Mental Health & Neuro Sciences (NIMHANS), Bangalore - the authors have previously discussed the findings in other publications (1, 2). Certain important aspects of the findings from the studies are placed in perspective against similar world literature data. There are certain striking differences with respect to family history, comorbid patterns and course of illness as compared to the findings of studies from elsewhere in the world.

Prevalence

Epidemiological studies on adolescent OCD have shown varying rates ranging from 1% to 4%, possibly because of varying methodologies and sample sizes. The rates are similar to those in adults (3). In an epidemiological study of child & adolescent psychiatric disorders in urban and rural areas of

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Bangalore, India (4), 2064 children aged 0-16 yrs, were selected by stratified random sampling from urban middle-class, urban slum and rural areas. The screening stage was followed by a detailed evaluation stage. The results indicated an OCD point prevalence rate of 0.1 per cent among children aged 4-16 years. A study involving 13-16 year old, 1100 high school children in Bangalore showed a point prevalence rate of 1.45% and 5.18% respectively for clinical and subclinical OCD respectively (5). The children were assessed by a psychiatrist using the Children Yale-Brown Obsessive-Compulsive Scale (6) and the Diagnostic Interview for Clinical Assessment of Children and Adolescents- Revised (7). The prevalence rate of 1.45% is comparable with the 1% and 1.9% rate reported by Flament et al. (8) and Whitaker et al. (9) respectively. This however is not consistent with the somewhat-higher rate of 3% and 3.56% reported in studies by Zohar et al. (10) and Valleni-Basile et al. (11) respectively. Another point of departure, is a much lower rate of 0.1% reported in the epidemiological study from India (4).

In the Indian epidemiological study, the age range of the sample was large, assessments were done by trained lay interviewers in the first stage and no specific instruments for OCD were used. In the study involving high school children interviews were done by an experienced clinician with a range of instruments specifically meant for diagnosis of OCD. The differences in the personnel involved in interviewing, the instruments employed and the characteristics of study population may explain the very low rate reported in the Indian epidemiological study. In the child and adolescent clinic settings of NIMHANS, there were just 16 cases of OCD between 1977 and 1985 (12) and this number rose to 195 cases in the period 1998-2006 (NIMHANS hospital records). This increase over the decades could be related to an

increased awareness both on the part of the patients and largely on the part of the clinicians.

Gender

In all the studies of OCD in children and adolescents reported from India, males have outnumbered female subjects (13-16). The proportion of male subjects has ranged from 63% to 85%. This male preponderance in juvenile OCD is consistent with the male predominance reported in most clinical studies of juvenile OCD (3). This finding is however inconsistent with the findings of ECA (17) and with that of a review of 11 adult OCD studies who found a slightly more female preponderance in adult OCD (18). Women appear to develop OCD slightly more often than men do as per most studies. The male preponderance in juvenile OCD may be due to the possibility that males develop OCD at a younger age than do females to justify the argument that gender distribution in OCD is developmentally sensitive.

Family History

A family study of OCD examined whether juvenile OCD was familial and whether the rate of Tourette Syndome (TS) and tic disorders was higher among relatives of patients with OCD than among relatives of control subjects (13). The study assessed first-degree relatives of 35 juvenile OCD probands (age = 16 years) and 34 matched psychiatrically unaffected subjects. Age corrected morbid risk was calculated. The morbid risk for OCD among relatives of OCD probands was about 5%, while none of the relatives of unaffected control subjects had OCD. TS was not diagnosed in any of the relatives of either OCD probands or control subjects. Most juvenile cases of OCD were nonfamilial and unrelated to tic disorders, while only a few were

familial. Limitations of this study were that the sample size was relatively small and interviewer was not blind to the proband status.

Available family studies suggest that juvenile OCD is highly familial with studies reporting as high as 25% relative risk in relatives of affected children (19-24). The risk in the Indian study was much lower compared to the studies from other parts of the world. There could be several possible reasons for such a difference. First, some forms of OCD may be genetically transmitted, while others are not. The heterogeneity of OCD may explain the high prevalence among relatives reported in previous studies. Subjects in other studies were largely severely and chronically ill whereas patients in the Indian study were self-referred, moderately ill, had a relatively shorter duration of illness, and were ascertained from the general child psychiatric services. If severity and chronicity are related to familiality, then the differences in rates of OCD across studies is possibly understandable. There is some evidence that phenotypic variability in OCD might be contributing to the variability in rates across studies (25, 26). Second, it is also possible that families with multiple affected members are more likely to present to specialized clinics, which may have, at least in some studies affected the rates of OCD in relatives. Third, the low rate could be because OCD was present only in parents and not in siblings. It is evident that siblings are less likely to have passed the risk period for developing OCD.

The absence of association between OCD and TS in the Indian study assumes importance in the light of findings from other studies, which suggest that OCD is a variant expression of the same factors that are important for the expression of TS and chronic tic disorders (27-29). Samples that reported

relationship between OCD and TS had severe OCD; if severity was to predict familiality and vice versa, the absence of TS in relatives of OCD probands is perhaps understandable, because the rate of OCD was itself very low. There is some evidence that high rates of TS and tic disorders are found among relatives of probands who had a family history of OCD than those without such a family history (20). Is the lack of familial relation between OCD and TS a true cross-cultural difference in the expression of the common factors that are important for manifestation of both OCD and TS? In other words, is the phenotypic expression in the form of TS uncommon in Indian setting? What factors determine the different phenotypic expression of a possible common genotype is, however, a matter of great speculation.

Phenomenology

It was believed until recently that OCD was rare in children and adolescents. It is now well known that 30%-50% of adults with OCD have onset of their symptoms during childhood or adolescence (18). In the background of the recognition of occurrence of OCD in children and adolescents, several studies have examined the clinical presentation of OCD during childhood and adolescence in various cultures (3). A study by Khanna and Srinath was one of the earliest studies to systematically examine the clinical profile of OCD in children in comparison with the OCD in adults (12). Hospital records of 16 children with clinical diagnosis of OCD were compared with those of 396 adult cases with OCD. Obsessive-compulsive phenomena were compared using the classificatory system that split obsessions and compulsions according to form and content (30). In this sample, obsessions were less frequent compared to compulsions. Obsessions were present in 62% of the children compared to 100% in adults whereas compulsions were present in

86% of the children compared to 66% in adults. Thoughts of harm, religion, and impersonal images were significantly more commonly reported. Compulsions involving washing and specific activities were more common compared to adults. As a theme specific activities included praying, touching, counting walking and spitting. Coming to the form of obsessions, obsessive fears and doubts were the commonest. Among compulsions, rituals defined as specific observable kinds of behaviors repeated in a set precise manner based upon arbitrary rules often felt to have a symbolic or quasi-symbolic significance were the most prevalent. This study demonstrated that there were some phenomenological differences between childhood and adult OCD but suffered from a retrospective design and small sample size.

Recent studies from India have examined the phenomenology of OCD in children using the children's version of the Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the instrument that is widely used all over the world (6). In a study of 58 children and adolescents all aged 16 years and below, contamination obsessions were the commonest (62%), followed by obsessions related to aggression (57%), symmetry (34%), sex (22%), religion (22%), somatic (12%), and hoarding (7%) (15). Regarding compulsions, cleaning and washing was the commonest (69%) followed by repeating (52%), checking (47%), ordering (29%), counting (15%), and hoarding (7%). The miscellaneous obsessions and compulsions were present in 65% and 47% of the subjects respectively. In another study, that examined the phenomenology of OCD in 39 children and adolescents, obsessions in the decreasing order of frequency were contamination fears (82%), pathological doubts (41%), religion (41%), aggression (38%), symmetry (36%), sex (26%) and hoarding (8%) (16). The compulsions included washing/cleaning rituals (67%),

repeating (56%), checking (44%), ordering/arranging (26%) and hoarding (10%). In this sample, miscellaneous obsessions and compulsions were present in 38% and 67% of the subjects respectively. The phenomenology of OCD in these studies is similar to that reported in a group of 70 young patients at the National Institute of Mental Health (NIMH), USA (31). In the NIMH study, predominant obsession was fear of dirt/germs (40%) followed by danger to self/others (24%), symmetry (17%), and religiosity (13%). The major compulsions in the order of decreasing frequency were washing rituals (85%), repeating (51%), checking (46%), touching (20%), ordering (17%), counting (18%), and hoarding (11%).

In one study (16), the phenomenology in juvenile OCD subjects (n = 39) was compared with that of adult-onset OCD subjects (n = 105) and juvenile-onset adult OCD subjects (n = 87), in view of the previously reported findings that juvenile OCD could be phenotypically different from adult OCD (32,33) and juvenile-onset adult OCD (34). In the multinomial logistic regression analysis involving the three groups of subjects, the obsessions related to contamination and compulsions related to checking and miscellaneous types were positively associated with juvenile OCD compared to adult-onset OCD. Similarly, compared to juvenile-onset adult OCD, contamination obsessions and miscellaneous compulsions were positively associated with juvenile OCD. In the comparison involving juvenile-onset adult OCD with adult-onset OCD, checking compulsions were negatively correlated with adult-onset OCD. In addition, the mean Y-BOCS score was greater in the juvenile OCD and juvenile-onset adult OCD subjects compared to the adult-onset OCD subjects suggesting greater severity of OCD in the juvenile groups. The variations in the clinical manifestations support developmental variability in the expression

of OCD. However, they are not consistent with specific variations reported in previous studies (33, 34). For example, OCD in juveniles was associated with a higher frequency of aggression/catastrophic obsessions, hoarding and saving compulsions (33). Sexual obsessions were selectively more prevalent in adolescents compared with children or adults. It is possible that sexual and aggressive obsessions were underrepresented in this sample due to the fact that the subjects kept them secret because of embarrassment and possible guilt associated in revealing them. However, there could also be a true cross-cultural variation in the phenotypic manifestation of OCD.

Comorbidity

Psychiatric comorbidity is common in adults with OCD. Similarly, studies of juvenile OCD have found high rates of comorbid major depression (10%-73%), anxiety disorders (26%-76%), and tic disorders (17%-59%) (14). Three studies have systematically examined the comorbidity in juveniles with OCD in India (14-16). Rates of comorbid major depression, dysthymia, and bipolar disorder have ranged from 14%-23%, 0%-2%, and 0%-2% respectively. Among anxiety disorders, rates of panic disorder, social phobia, specific phobias, overanxious disorder and separation anxiety disorder ranged from 0%-6%, 0%-13%, 5%-7%, 0%-7%, and 5%-7% respectively.

Of considerable interest is the comorbid relationship between tic disorders, disruptive behavior disorders and juvenile OCD. Rates of TS have varied from 11%-15% and that of other tic disorders from 17%-59% (14). In the three studies mentioned above, rates of TS and chronic tics are in the range of 8%-11% and 2%-23% respectively. In the follow-up study by Leonard et al. TS was present in 15% of the sample and any tics in 59% of the sample (35). The rate

of TS in the Indian juvenile OCD samples is somewhat comparable to the rates in previous studies, but the overall rate of tic disorders and, in particular, chronic tics are somewhat lower. In a recent study, clinical profile of patients with both OCD and tics was examined in three groups of OCD subjects (16). The groups included juvenile OCD (n = 15), juvenile-onset adult OCD (n = 38) and adult-onset OCD (n = 34). Miscellaneous compulsions such as touching, tapping, rubbing, blinking, staring etc (73% vs. 45% vs. 32%) and pathological doubts (40% vs. 13% vs. 9%) were overrepresented in the juvenile OCD group compared to the other two groups. The rate of attention-deficit hyperactivity disorder (ADHD) was significantly higher in the juvenile OCD compared to the other two groups (26% vs. 3% vs. 0). The miscellaneous compulsions of the type reported in this study were also reported in previous studies of OCD patients with tics (36, 37) but the obsessions are not similar to the ones reported in other studies that found mainly excess of aggressive, sexual, and symmetry obsessions (36,38). Further, the elevated rate of ADHD in juvenile OCD with tics support the previous observations that ADHD, tics and OCD commonly co-occur in juvenile OCD (35,39) and are possibly interrelated sharing a common pathophysiology (40).

Few recent studies have reported a novel pattern of comorbidity with disruptive behavior disorders, particularly ADHD. ADHD is considered by some to be a developmental marker of juvenile OCD (41). In the study by Leonard et al. (42) the rate of ADHD was 26% and in the studies by Geller and colleagues (33, 41, 43), the rate of ADHD was as high as 57%. In the three Indian studies, rates of ADHD ranged from 3% to 18%. The rates of ADHD in Indian samples are considerably lower than the rates reported in previous studies. The samples in the previous studies by Geller and colleagues were

recruited from a specialized pediatric OCD program, whereas the Indian samples were largely 'self-referred' and this difference in the ascertainment method might possibly explain the variation in the rates across the samples. However, at least in one study (16), the 18% rate of ADHD was higher than the 5%-10% rate reported in community samples (44, 45). The elevated rate of ADHD in juvenile OCD in this study is consistent with the findings of previous studies (33, 41, 43) although the rate of ADHD is much lower than the 51%-57% (children) and 36%-39% (adolescents) reported in the studies by Geller and others (33,43). Overall, the elevated rate of ADHD in this study supports the argument that ADHD may represent a developmental marker of juvenile OCD.

In the study by Jaisoorya et al, juvenile OCD was compared with adult-onset OCD, using multinomial logistic regression analysis (16). There was positive association of chronic tics, ADHD, major depressive disorder, and body dysmorphic disorder (BDD) with juvenile OCD. The TS showed an almost significant association with juvenile OCD. The BDD also had a positive association with juvenile-onset adult OCD. In addition regression analysis (juvenile-onset adult OCD vs. adult-onset OCD), showed positive association between social phobia, chronic tics and MDD and juvenile-onset adult OCD. These findings suggest that there are age-specific correlates of the disorder across the life cycle. Further, the findings suggest that OCD in juveniles is perhaps a developmental subtype of OCD with specific correlates such as high rate of ADHD and tic disorders (32, 33, 43).

Course and Outcome of Childhood OCD

The follow-up studies of OCD in children and adolescents have reported

low rates of remission. For example, in a 2-7 year follow-up study of 54 children and adolescents treated with clomipramine, 43% still met diagnostic criteria for OCD and only three (6%) were in true remission (42). Two Danish studies (46, 47) and a German study (48) also reported low rates of recovery. Similarly, studies of adult OCD have reported worse course in those with early onset of illness (49, 50). However, studies on long-term course and outcome of OCD in juveniles are few and many have small sample sizes. We discuss here a 2-9 year follow-up study of 58 children and adolescents from India that was reported recently (15).

All the subjects who had DSM-III-R OCD and aged 16 years and below at the time of first consultation were followed up employing a catch-up longitudinal design. The subjects were treated at the Child and Adolescent Psychiatric Services of the NIMHANS, Bangalore, India between 1992 and 1998. There were 68 subjects with DSM-III-R OCD, of which 58 subjects were (85%) followed up for a mean period of 5 years after initial consultation. Evaluations were done by senior psychiatrists using structured instruments and the Y-BOCS and its child version. The subjects were largely 'self-referred' (93%) and 'drug-naïve' (90%) at the time of consultation. None had received any form of psychotherapeutic intervention and none were treatment refractory at the time of first consultation. The patients attending specialized clinical services elsewhere in the world are generally 'referred' and tend to be severely ill, whereas patients attending the psychiatric services in India are largely 'self-referred' and 'drug-naïve'.

During the interval period, most were treated with medications; 72% were adequately treated (10 week trial of adequate doses of serotonin reuptake

inhibitors) and seven of them (12%) with a combination of medicines and exposure and response prevention). At the time of follow-up only 29% were still receiving medication. The median duration without any treatment at the time of follow-up was 49 months. The course and outcome of the sample is given in the Table 1. In summary, 62% of the subjects were in full remission or had 'no OCD' outcome (Total Y-BOCS score = 0 to 3) and only 21% had clinical OCD (met DSM-III-R criteria & Y-BOCS > 15). The median time to achieve full remission was 24 months and subjects were symptom free for a mean of 41 months prior to follow-up assessment. However, the most significant finding is that 28 subjects (48%) were in true remission (full remission and not on any treatment) and were not any treatment for a mean period of 58 months.

Stepwise logistic regression analysis was performed to identify the

Table 1: Course and outcome of obsessive-compulsive disorder (OCD) in 58 children and adolescents

Course	Outcome at follow-up			
	No OCD*	Subclinical OCD	Clinical OCD	Total
No OCD	31 (53)	0	0	31 (53)
Subclinical OCD	3 (5)	10 (17)	0	13 (22)
Episodic OCD	2 (3)	0	2 (3)	4 (7)
Chronic OCD	0	0	10 (17)	10 (17)
Total	36 (62)	10 (17)	12 (21)	58 (100)

Values are given as n (%).
* The 36 subjects with 'no OCD' outcome include 28 subjects (48%) who were in true remission

Adapted from Reddy et al. (15)

predictors of full remission (no OCD outcome). Of the many predictors, only duration of follow-up and age-at-onset emerged as significant predictors of full remission; these two predictors correctly classified 77% of the total group. The odds of younger subjects having full remission or no OCD outcome was 1.5 times that of older subjects. Those who had 'no OCD' at follow-up had earlier age-at-onset of illness.

The main finding of the study is a high rate of 'true remitters' (48%) with only 21% having clinical OCD. The high rate of 'true remitters' is in sharp contrast to the 6% rate in the study by Leonard and others (42). The rate of clinical OCD (21%) at follow-up is low compared to the high rates of clinical OCD (35%-68%) reported in previous studies (42, 46-48, 51). The course of OCD in this Indian study was also favorable compared to the course in some of the previous studies, which used similar definitions of course. The findings are compared in the Table 2.

The better course and outcome in this Indian study could be due to several

Table 2: Comparison of course of obsessive-compulsive disorder (OCD) in different samples

Course	Thomsen, 1995 (n = 47)	Thomsen & Mikkelsen, 1995 (n = 23)	Wewetzer et al., 2001 (n = 55)	Reddy et al., 2003 (n = 58)
No OCD	13 (28)	4 (17)	16 (29)	31 (53)*
Subclinical OCD	12 (25)	8 (35)	15 (27)	13 (22)
Episodic OCD	10 (21)	11 (48)	17 (31)	4 (7)
Chronic OCD	12 (25)	11 (48)**	7 (13)	10 (17)

Values are given as n (%).
* $P < 0.017$ (after Bonferroni correction).
** Includes episodic or chronic OCD

Adapted from Reddy et al. (15)

reasons. First, the sample was largely 'self-referred', 'drug-naïve', moderately ill, with relatively low rate of comorbidity (55%). This may explain better prognosis. For example, in the study by Leonard et al. (42), all the subjects were severely and chronically ill with history of treatment resistance in 75% of them and 100% comorbidity. Second, a low rate of tic disorders (16%) and ADHD (3%) could have contributed to better prognosis. Lifetime history of tic disorders and ADHD has been associated with a worse OCD outcome. In the study by Leonard et al. 59% had tic disorders and 26% had ADHD (42). Lastly, whether there are true cross-cultural differences in the course and outcome need to be considered and addressed in future studies.

The study findings suggest that juvenile OCD, at least, in largely self-referred, drug-naïve clinical samples has a good prognosis. The findings are generalizeable to psychiatric hospital settings across India and perhaps to general psychiatric practice settings in other countries as well. It is possible that poor outcome reported in many previous studies are not applicable to the majority of young OCD subjects who do not get referred to tertiary care or specialized services. The study findings have important implications. First, this study reports favorable prognosis in a disorder that is otherwise considered to be a chronic, relapsing illness. This observation is supported by the findings of high rates of remission in epidemiological studies of juvenile OCD (10, 11). Second, that such a high rate of remission was found in the sample treated with mainly medications is reassuring because in countries like India cognitive behavior therapy regarded as the treatment of choice (52) is not easily available for a majority of patients. One major concern in the literature is about the high rates of relapse following discontinuation of medication (53). That nearly a half of the sample were true remitters and were not on any medication for

prolonged period implies that substantial proportion of juvenile OCD subjects perhaps do not require ongoing treatment for indefinite period to prevent relapses. However, it needs to be mentioned here that the follow-up studies of this kind typically have no untreated control group and therefore, the benefits of treatment over no treatment cannot be clearly established. Lastly, early age-at-onset of OCD was associated with better outcome. This finding needs replication in larger samples. It is possible that early onset OCD is a subtype of juvenile OCD with better prognosis.

Summary

The research on OCD in children and adolescents from India is broadly consistent with the world literature although there are certain differences. The data suggests that juvenile OCD could be a developmental subtype of the disorder (16). There was positive association of chronic tics, ADHD, major depression and BDD with juvenile OCD. Outcome of juvenile OCD was favorable with high rates of remission (15). Although this is not very much consistent with the individual published studies on course and outcome of juvenile OCD, a recent meta-analysis of OCD in children confirmed the finding that long-term outcome may be favorable (54). The meta-analysis predicted poor outcome in those with early onset, longer duration of illness and inpatient status.

The data from studies conducted in India suggests that 1) comorbid patterns are somewhat different with low rates of disruptive behavior disorders and tic disorders, and 2) that OCD in children could have a better long-term prognosis, particularly in those with very early onset. There is also some preliminary data that rates of familiality are low compared to the

findings of other studies (13). It is also interesting to note that there are no reported cases of "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)" from India although there are reports of OCD in rheumatic chorea (55) and rheumatic heart disease (56).

The data from Indian studies should be interpreted keeping in mind certain obvious limitations. For example, all the studies are cross-sectional and the family study had small sample size and the interviewer was not blind to the proband status. The long-term course and outcome study was retrospective in nature with a catch-up longitudinal design. There is a need for further systematic examination of all the juveniles with OCD with respect to their symptom profile, comorbidity, longitudinal course and treatment response. Longitudinal studies should evaluate neuropsychological functioning and psychosocial outcome and not just symptomatic outcome. There is no published data with respect to the applicability of CBT to Indian children particularly with respect to whether there is a need to modify reattribution strategies keeping in mind the possible cultural differences. Relationship between ADHD and pediatric OCD needs further exploration considering recent publication of some impressive data supporting the familial relationship between pediatric OCD and ADHD (57, 58).

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Chapter 8

Long-term Course and Outcome of Obsessive-Compulsive Disorder

Y C Janardhan Reddy and Suresh Bada Math

Introduction

Obsessive-compulsive disorder (OCD) is a common mental illness with prevalence rates ranging from 1% to 3 % in the general population (1-5). Effective pharmacological and non-pharmacological treatment options are now available for OCD. However, there is a paucity of data on the long-term course and outcome of OCD. In this chapter, an attempt is made to review the available data on the long-term course and outcome of OCD by separately examining the data from the older, naturalistic follow-up studies and from the newer studies in which patients are likely to be treated with serotonin reuptake inhibitors (SRIs), cognitive behavior therapy (CBT) or a combination of the both.

The prevailing notion about the course of OCD is that it runs a chronic course with waxing and waning severity of symptoms but rarely remits completely (6-8). In other words, once a patient develops OCD, symptoms are continuously present with varying degrees of intensity over time; they rarely become symptom free or recover from illness. We review in this chapter data

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from both the older naturalistic follow-up studies and recent longitudinal studies to examine if the evidence is supportive of this often repeated claim in literature (Table 1). The follow-up studies of OCD in children and adolescents are not reviewed in this chapter and the readers may refer to an excellent review by Stewart and colleagues (9).

Naturalistic Follow-up Studies from the Pre-SRI/CBT Era

In one of the earliest follow-up studies of OCD published in the year 1936, Lewis observed improvement in 66% and recovery in 32% of the patients (10). A few other studies were also published in the '30s (11, 12) and '50s (13-17) with recovery rates ranging from 6% to 39% and improvement rates from 27% to 58%. The study by Pollitt deserves a special mention because of its interesting observations (16). Pollitt reported 3 months-15 years (mean 3.4 years) outcome of 101 obsessional patients. Of these 34 were leucotomized. Of the remaining 67 non-leucotomized patients, 40% were either symptom free or had mild symptoms with normal social adaptation. Of the patients who had improved, a majority did so within the first two years. Those who improved had a shorter duration of illness and as the duration of illness increased, fewer patients with good prognosis were found. The mode of recovery was gradual and was seldom smooth. However, a majority of the patients had an episodic course with exacerbations usually lasting less than a year.

In the 1960s, three important follow-up studies were published by Grimshaw (18), Ingram (19) and Kringlen (20) with varying follow-up periods. The study by Grimshaw reported highest recovery rate of 40% out of the 97 patients studied after a mean follow-up period of 5 years. Overall, 77% had

fully adapted socially. A Chinese study of 87 patients followed-up over 1-14 years reported recovery in 20%, improvement in 36% and unimproved status in 44% (21). In a review of 13 naturalistic follow-up studies, Goodwin et al concluded that the data justified a certain measure of optimism about the 'natural' course of obsessional disorder (22). It was evident that spontaneous remissions occurred rather often, with recovery in about a third of patients. The authors made some valid observations regarding the relationship between outcome and the baseline severity of illness. Those who required hospitalization generally had a chronic course with periodic flare-ups and a tendency for the illness to wane gradually in severity over many years; no more

Table 1: Outcome of OCD in older naturalistic follow-up studies

Study	Sample size	Follow-up in years	Full- remission, %	Improved, %	Unimproved, %
Lewis (10)	50	> 5	32	34	34
Langfeldt (12)	27	1-11	26	41	33
Luff et al (11)	49	3	39	27	34
Rudin (17)	130	2-26	12	26	61
Muller (15)	57	15-35	28	50	22
Balslev-Olesen et al.(13)	52	0-8	6	58	37
Hastings (14)	23	6-12	13	40	47
Pollitt (16)	67	0-15	24	48	28
Ingram (19)	46	1-11	9	30	61
Grimshaw (18)	97	1-14	40	24	35
Kringlen (20)	85	13-20	4	45	45
Lo (21)	87	1-14	20	36	44
Skoog & Skoog (24)[a]	144	40	20	63	17

[a] full recovery = 20%, recovery with subclinical symptoms = 28%,
overall improvement = 83% (including full and recovery with subclinical symptoms)

Table modified after Goodwin et al (22)

than one third improved symptomatically. On the other hand, outpatients appeared to have a rather good prognosis, as many as 60% to 80% were asymptomatic or improved one to five years after diagnosis.

Overall, the older naturalistic follow-up studies of OCD report a somewhat better prognosis than what is generally believed. These studies, however, suffered from a number of methodological limitations and they need to be kept in mind while interpreting the data. The limitations include a lack of standardized operational criteria to determine diagnosis, diagnosis and outcome based on chart reviews, a lack of structured interviews, retrospective study designs, and a lack of consensus on definitions of relapse, recovery and remission (23). Added to these are the differences in study populations (inpatient/outpatient), inclusion of lobotomized patients, and highly varying duration of follow-up periods both across and within the individual studies (23, 24).

In the light of some of the limitations of the previous studies, Skoog and Skoog (24), in the year 1999, published a landmark 40-year follow-up study of patients with OCD. Two hundred and fifty one patients admitted to the Sahlgrenska University Hospital, Goteborg, Sweden between 1947 and 1953 formed the sample of the study. The same clinician reexamined them after nearly 5 decades between 1989 and 1993. The study was based on those who survived for at least 3 decades after first examination. Of the original sample, 75 had died (including six suicides), and 32 were lost for follow-up because of other causes. The study in the end reported findings on 144 patients (out of surviving 176 patients) on whom data could be collected. The diagnosis of OCD was based on the criteria of Schneider (24, 25); however, 86% of the

patients also fulfilled the DSM-IV criteria (6). Improvement was observed in 83% of the patients, including recovery (absence of clinically relevant symptoms for the last 5 years or more) in 48% (complete recovery, 20%; recovery with sub-clinical symptoms, 28%). Among those who recovered, 38% had done so in the first decade. Overall, a majority of those improved did so within a decade of the onset of illness. Nearly a half of the patients had illness for more than 30 years. Early age at onset, presence of both obsessions and compulsions (mixed subtype), low baseline social functioning, chronic course and magical obsessions were associated with poor prognosis.

Although an improvement rate of 83% and a recovery rate of 48% in the study by Skoog and Skoog is suggestive of an optimistic outcome, some sobering qualifiers temper it. Only one fifth of the cohort achieved full recovery; among those who recovered early, about half did not have relapses after 3 decades but a fifth had relapses after a remission of more than 2 decades. Thus, early recovery, while correlated with good prognosis, does not exclude the possibility of a very late relapse. This study has certain important limitations. The subjects were all inpatients, only a small proportion of the follow-up assessments were done by direct personal examination (n = 23), a high attrition rate and a possible difficulty in the recall of the events between assessments.

Recent Long-term Follow-up Studies

Some of the recent studies that employed standardized diagnostic criteria reported chronicity of the disorder with very low rates of remission (26, 27). However, long-term follow-up studies of patients treated with SRIs or CBT are few despite the widespread use of these treatments in OCD (Table 2). One

of the earliest studies to report on the long-term outcome of adult OCD subjects treated with SRIs was by Orloff et al (28). The records of 85 patients who had first been evaluated at least 1 year previously were reviewed. At follow-up, their mean Yale-Brown Obsessive-Compulsive (Y-BOCS) (29, 30) score had decreased from 23.7 (SD, 6.7) to 10.1 (SD, 7.0). Twenty-eight patients (33%) had Y-BOCS scores that had decreased by more than 75%, 26 patients (31%) had scores that had decreased 50%-75%, and 24 patients (24%) had scores that had decreased 25%-49%. Overall, 87% of the patients had responded to treatment. However, no predictors of improvement were found. In this sample, 84 patients (99%) had at least 10-week trial of an SRI and 36 patients (42%) had received behavioral treatment. Most patients, although improved at the end of 1-3 years, were still taking medication at follow-up.

Eisen et al reported a 2-year prospective follow-up of 66 DSM-III-R OCD patients, in which over two thirds had received medium-to-high doses of at least one SRI for = 12 weeks (23). Only 18% of the subjects received an adequate trial of CBT (20 hours of CBT). The study found a 47% probability of achieving at least partial remission (subclinical symptoms, Y-BOCS = 8-15) and a 12% probability of achieving complete remission (essentially no symptoms, Y-BOCS = 7) over a 2-year period. In those who achieved remission, the probability of relapse (Y-BOCS = 16) was 48%. In terms of improvement, only 54% of the subjects had a = 25% reduction in baseline Y-BOCS score. The findings of this study indicate that patients may improve with an SRI, but very few remit.

In a 5-year prospective follow-up of 100 patients with DSM-III-R OCD (31), results were somewhat similar to those in the study by Eisen et al (23). The

Table 2: Long-term outcome of OCD in patients treated with SRIs, CBT or both

Study	Sample size	Follow-up in years	Full remission, %	Partial remission, %	Clinical OCD, %
Orloff et al. (28)[a]	85	1-3	33	55	12
Eisen et al. (23)[b]	66	2	17	35	48
Steketee et al. (31)[b]	100	5	20	50	30
Hantouche et al. (32)[c]	155	1	77		23
Reddy et al. (35)[d]	75	11-13	43[f]	33	24
Rufer et al.(57)[b]	30	6-8	27	17	57
Van Oppen et al. (58)[e]	102	5	43	32	25
Catapano et al. (34)[b]	79	3	22	34	44

SRIs = Serotonin Reuptake Inhibitors, CBT = Cognitive behavior Therapy

[a] full remission = reduction in Y-BOCS by more than 75%, partial remission = reduction in Y-BOCS by 49%-75%, clinical = reduction in Y-BOCS by less than 25% or scores higher than baseline

[b] full remission = Y-BOCS $\leq$ 7, partial remission = Y-BOCS 8-15, Clinical (in episode) = Y-BOCS $\geq$16

[c] global improvement in 77% (30% reduction in NIMH-OC score and Global Assessment of Functioning score $\geq$ 70)

[d] full remission = Y-BOCS score $\leq$ 3, partial remission = Y-BOCS score 4-15, clinical = Y-BOCS $\geq$16

[e] full remission = Y-BOCS score $\leq$ 12 and an improvement of $\geq$ 7 compared to the baseline

[f] 53% if full remission is defined as Y-BOCS $\leq$ 7

probability of full remission (Y-BOCS = 7) was low at 1 year (15%) and remained low even at 5-year follow-up (22%). The likelihood of partial remission (subclinical symptoms, Y-BOCS = 8-15) was considerably higher (53%) after 5 years. In this study, as in the one by Eisen et al (23), most full recoveries occurred within 1 year of intake and nearly all partial recoveries occurred within 2 years. The authors concluded that most improvements occur within 2 years and thereafter remissions are unlikely. Partial remission was predicted by being married and having lower global severity scores at

intake. Authors speculated that being married might signal less severe illness or that the partners may have facilitated the change. Depression was marginally predictive of poorer outcome. Interestingly, those treated with SRIs had poorer outcome than those who were not treated with SRIs. They surmise that association between treatment with SRIs and poor outcome may be spurious since it is very likely the result of treatment bias in naturalistic studies where sicker patients typically receive more intervention. One of the problems in concluding the effect of treatment on outcome in this study is that there are no details of the treatment received by the subjects and there is no data as to whether those treated with SRIs or CBT were sicker compared to the rest.

In a French national study, 155 patients with DSM-III-R OCD who were severely and chronically ill with associated depression were followed up over a 12-month period; a majority of the completers had been treated with drugs (84%) and only a minority had received behavior therapy (19%) (32). A majority of the subjects was largely compliant with treatment (84%) and global improvement was observed in 77% of the patients treated. Lack of insight was the best predictor of treatment resistance. The outcome criteria employed in this study are somewhat different from those in other studies making comparisons across studies difficult.

A 1-year naturalistic follow-up study of DSM-III-R OCD patients specifically examined the effect of comorbid depression on outcome (33). The study had a sample size of 74, all treated with a combination of an SRI and behavior therapy; 73% of the subjects had comorbid depression. Patients with good prognosis showed no depressive symptomatology at follow-up and depressive symptoms seemed to have disappeared with the improvement in

OC symptoms. In other words, depression persisted in those who had not improved with respect to OC symptoms. The authors concluded that comorbid depression did not have any major influence on the prognosis of OCD.

Recently, a group of researchers from Italy reported the findings of a 3-year prospective follow-up of 79 DSM-III-R OCD patients treated with serotonin reuptake inhibitors (34). During the follow-up period, the clinical status was evaluated monthly in the first year and bimonthly thereafter. They used the definitions of remission and relapse employed by Eisen et al (23) and Steketee et al (31). At the end of 3 years, 44% of the 55 completers still met criteria for OCD (YBOCS = 16), 34% were in 'partial remission' and only 22% were in 'full remission'. About a third of the sample was SRI resistant, treated with adequate doses of at least three SRIs. The cumulative probability of achieving at least partial remission at the end of 3 years was 65%. The probability of full remission was 38%. For those who achieved at least partial remission, the probability of subsequent relapse (YBOCS > 16 for at least 1 week after achieving remission) was 60%. In agreement with some of the previous studies (23-31), most remissions occurred within the first 2 years with less likelihood of remissions thereafter. Longer duration of illness, greater severity of illness and schizotypal disorder predicted poor outcome. The authors concluded that their findings support the idea that OCD is a chronic disorder and that pharmacological treatment, has, in most cases, only a limited efficacy. Some important limitations of this otherwise methodologically rigorous study need to be kept in mind. Subjects were severely and chronically ill, and the study was carried out at a specialized university center with its attendant referral bias towards severely ill patients. Moreover, the sample had a high rate of comorbidity with personality disorders (70%).

It is evident that there are very few naturalistic follow-up studies involving representative OCD subjects followed-up over a very long period. The major limitations included small sample sizes, shorter follow-up periods, and inclusion of severely ill patients who were often clinically referred and hospitalized. Considering these limitations, an Indian study reported findings of an 11- to 13-year follow-up of 75 OCD subjects satisfying DSM-IV criteria for OCD (35). In this retrospective cohort study with a catch-up longitudinal design, a majority was self-referred (84%), drug naïve (72%), outpatients (80%) and was ill for = 24 months (71%). Three-fourth of the subjects received an adequate trail with SRIs (76%), and only a minority (15%) received additional behavior therapy involving exposure and response prevention. Median duration of treatment was 23 months. However, 71% of the subjects were not on any treatment at the time of follow-up evaluation, for a median duration of 122 months. Only about a fourth of the sample (24%) had clinical OCD (Y-BOCS score > 15) outcome at follow-up; the remaining had either 'no OCD' (Y-BOCS score = 3) (43%) or 'subclinical OCD' (Y-BOCS score, 4 to 15) (33%). Median time to reach 'no OCD' and 'subclinical OCD' status was 42 months and 84 months respectively. Interestingly, 37% of the subjects were in true remission ('no OCD' and not on any treatment) for a very long period (median, 132 months). Regarding course 40%, 25%, 11% and 24% of the subjects had 'no OCD' (no symptoms after recovery from the index episode), 'subclinical OCD' (mild symptoms that did not cause significant distress or impairment), 'episodic OCD' (clear remissions and relapses), and 'chronic OCD' (persistence of symptoms for most of the course causing significant distress and impairment) respectively. In the multinomial logistic regression analysis, 'mixed' subtype of OCD (presence of both obsessions and compulsions), and any Axis I lifetime comorbidity predicted worse outcome.

The findings of this Indian study are most optimistic compared with the findings of other recent follow-up studies of adult OCD (23, 24, 28, 31, 34, 36). The most striking finding of the study is the very high rate of complete remission (43%) where complete remission is absence of symptoms (Y-BOCS score = 3). The rates of full remission in the other studies, defined rather liberally (Y-BOCS score of < 8) ranged from 17% to 22%. If the Y-BOCS score of < 8 is applied, the rate of full remission in the Indian study raises to 53%. There are several possible reasons for favorable outcome. They include, sample characteristics (outpatients who were largely drug-naïve and self-referred), a shorter duration of illness, and a relatively low rate of comorbidity (lifetime, 39%). The subjects in other studies perhaps represented a subgroup of OCD subjects who were severely and chronically ill, with high rates of comorbidity, and poor treatment response. For example, in some recent studies (23, 28, 31, 34, 36), mean duration of illness ranged from 9 to 21 years with high comorbidity rates. On the other hand, Indian sample perhaps represented moderately ill, recent-onset OCD subjects. It is therefore, possible to speculate that the findings of this study are generalizeable to a large majority of OCD subjects who seek outpatient treatment at general psychiatric practice settings. The findings suggest a favorable prognosis in a disorder that is otherwise considered a chronic illness. To an extent, these findings are supported by a prevalence study of OCD in a large health maintenance organization that found that 43% of the subjects had no OCD at 38-month follow-up (37). Similarly, a 20-year follow-up of 22 OCD subjects in a Zurich community cohort reported recovery in 86% (38). The Indian study suggests that the findings in OCD follow-up studies perhaps depend on the types of sample studied and that the prognosis of OCD may be favorable in a large majority of OCD subjects who are treated as outpatients and are moderately

ill. A major limitation of this study is the catch-up longitudinal design using a retrospective cohort. The treatment was not controlled and a majority received only drugs. In a study of this kind, it is difficult to differentiate the long-term effects of treatment from the natural course of illness.

Long-term benefits of pharmacologic treatment

Despite the fact that SRIs and CBT are well established as effective treatments for OCD, there is very little controlled data on their efficacy in the long-term treatment. There is some data on the efficacy of sertraline and fluoxetine. In a double-blind placebo controlled study, responders to 12 weeks of fixed doses of sertraline or placebo were assigned to a double-blind fixed dose trial for an additional 40 weeks (39). At the end of 52 weeks, there was significant improvement in Y-BOCS and other global measures for the sertraline group compared with the placebo. In addition, 51patients who originally participated in the double-blind trial of sertraline or placebo continued to take sertraline in the open label phase for up to a total of 2 years (40). The efficacy was not only maintained over the 2 years but some modest additional improvements occurred. In the third study on sertraline, 223 patients who met criteria for response (25% fall in the Y-BOCS score) after 16 and 52 weeks of a single-blind trial of sertraline were randomly assigned to a 28-week doubleblind trial of 50-200 mg/day of sertraline or placebo (41). Sertraline had significantly greater efficacy than placebo in preventing dropout due to relapse or insufficient clinical response and acute exacerbation of OCD symptoms. There was no significant difference between the groups with respect to relapse rate possibly because of low incidence of relapses (<5% overall). This low rate of relapse may well be due to a sustained benefit of 52 weeks of therapy with sertraline, even after drug discontinuation, although

other studies (42-48) have suggested high relapse rates following discontinuation. These studies, however, had a shorter duration of treatment before discontinuation. Only about a third of the patients treated with placebo experienced an acute exacerbation of OCD symptoms within the 28 week double-blind phase, again reflecting the sustained benefit of 52-week drug therapy. There is therefore a possibility that prolonged treatment may prevent relapses even after discontinuation of drugs.

In a study of 50 patients with OCD who had previously responded to 12 months of high-dose fluoxetine, relapse rate was only 23% among those who discontinued treatment (49). Romano et al. assessed the efficacy of fluoxetine versus placebo in preventing relapse of OCD during a 52-week trial of 71 responders to 20-week treatment of fluoxetine (50). Patients who received fluoxetine did not differ significantly from the placebo group with respect to relapse rate (21% vs. 32%), but patients who received high dose fluoxetine had significantly lower relapse rate than those treated with placebo (17% vs. 38%). Overall, the relapse rates in patients treated for longer duration appear to be much lower than the 80%-90% relapse rate in studies (43-46) of shorter treatment.

Combination of CBT and drugs

Patients treated with medications alone have shown high relapse rates following discontinuation (43-48), whereas several prospective follow-up studies have demonstrated that improvement after CBT tends to persist with relatively low relapse rates (51). Nine prospective follow-up studies involving 223 patients conducted 1 to 6 years after behavior therapy reported improvement or much improvement in about 80% of the patients (52). A

meta-analysis of 6 studies with follow-up periods of 7-24 months demonstrated that gains were maintained up to 2 years after CBT (53). However, studies of much longer follow-up periods are important to know the long-term benefits of treatments. Such follow-up studies are few in OCD.

Although both CBT and SRIs are effective in treating OCD, only a few studies have compared the efficacy of combination of CBT + drugs with CBT and drugs alone. In the studies by Cottraux et al (54) and Hohagen et al (55) there was there was a short-term advantage of a combination of fluvoamine and CBT over CBT alone, particularly in those with predominant obsessions and comorbid secondary depression (55). However, in the follow-up study by Cottraux et al (56), there were no differences at the end of 48 weeks and 18 months.

A 6-year follow-up study of 34 OCD patients treated with a combination of exposure and clomipramine, reported that 74% (n= 25) were classified as 'improved' or 'much improved' in a self-rating scale (57). However, only 29% (n= 10) were drug-free throughout the follow-up period. In a study of long-term course of OCD, patients treated with SRIs and behavioral therapy were followed up for 1 to 5 years (mean = 2.5 years) to identify predictors of clinical outcome (36). Sixty outpatients meeting DSM-III-R or DSM-IV criteria for OCD received prolonged pharmacologic therapy with an SRI. Thirty-seven patients (62%) completed an adequate behavioral treatment. At long-term assessment, 37% (n = 22) of the patients were considered nonresponders (Y-BOCS >16 or < 35 percentage reduction in the score). A substantial number of OCD patients showed persistent disabling symptoms in spite of combined pharmacologic and behavioral treatment. Major benefit from behavioral

therapy was the improvement in ritualistic behaviors. Sexual/religious obsessions predicted poorer long-term outcome, whereas short-term response to SRI treatment failed to achieve predictive value in the long-term course of OCD.

A recent study followed up 30 out of 37 inpatients (81%) 6-8 years after treatment with CBT + fluvoxamine or CBT + placebo in a randomized double-blind trial (58). Throughout the naturalistic follow-up period, nearly all patients received additional CBT and/or medication. Response rates (> 35 percentage reduction in the Y-BOCS) in the short-term and long-term were 67% and 60% respectively. Full remission was seen in 27% of the subjects (n =8). Long duration of illness at baseline was associated with lesser likelihood of full remission. However, there was no significant difference in the outcome between the groups suggesting lack of superiority of combination treatment over CBT alone. Another recent article reported a naturalistic 5-year follow-up of 102 DSM-III-R OCD outpatients treated with either cognitive therapy or ERP alone or a combination of CBT (ERP or cognitive therapy) and fluvoxamine (59). There was no difference in the outcome between the groups again suggesting lack of superiority of combination of CBT + drugs. Overall, nearly three quarters of all patients fulfilled criteria for reliable clinical improvement (the cutoff point, Y-BOCS score = 7) in OCD symptoms and 54% of the subjects no longer met criteria for DSM-III-R OCD. Forty-three percent had recovered (= 12 and an improvement of = 7 compared to pretest score) and about a quarter continued to be symptomatic.

In addition to the four long-term follow-up studies described above (36, 57, 58, 59), three recent uncontrolled studies on combination therapy show some

interesting results. In the study by Biondi & Picadi (60), out of 10 patients treated with medication alone, eight relapsed whereas out of 10 patients treated with drugs and CBT, only 1 relapsed. In another study of 62 patients (61), long-term outcome after a mean of 17 months was better with behavior therapy and a combination treatment than with drugs alone. The third study by Kordon et al (62), followed up 74 patients, 37 were treated with CBT alone and the remaining 37 with CBT and drugs over a 2-year period. Of the latter, 17 discontinued drugs during the follow-up period, but there was no recurrence of symptoms suggesting CBT prevents relapses and therefore, drug discontinuation may be attempted in those treated with combination of CBT and drugs after stable remission.

The results of long-term follow-up studies of combination treatment have to be interpreted with caution. Firstly, sample sizes were relatively small resulting in poor statistical power to detect differences between two highly effective treatments for OCD and thus definite conclusions cannot be drawn from the negative findings. Secondly, nearly all patients in these studies have received additional treatments during the naturalistic follow-up periods and the outcome cannot be attributed only to original treatments.

Predictors of Outcome

Relatively few studies have examined the predictors of course in untreated patients with OCD. In the study by Pollitt (16), shorter duration of illness predicted better prognosis and as the duration of illness increased fewer patients with good prognosis were found. Goodwin et al (22) in their review of older follow-up studies reported that those who required hospitalization generally had a chronic course and no more than one third improved

symptomatically, whereas outpatients had a rather good prognosis with recovery/remission rates of 60% to 80%. They also reported mild illness, absence of compulsions, a short duration of illness, and good premorbid personality to be associated with a favorable prognosis. In the study by Ravissa et al (63), chronic course was associated with earlier onset, longer duration of illness, male gender, more severe compulsions and higher family loading for psychiatric disorders. The much longer study by Skoog and Skoog (24) identified early age-at-onset, presence of both obsessions and compulsions (mixed subtype), low baseline social functioning and baseline chronic course, and magical obsessions as predictors of poor prognosis.

In the naturalistic follow-up studies of patients treated with drugs or CBT, findings are not consistent. In the studies by Eisen et al (23) and Orloff et al (28) no predictors of outcome could be identified. The study by Steketee et al (31) reported being married and having lower global severity scores at intake as predictive of partial remission; depression was only marginally predictive of poorer outcome. However, in study by Zitteral et al (33), comorbid depression did not have any major influence on the prognosis of OCD. A 3-year prospective follow-up study of patients treated with SRIs found longer duration of illness, greater severity of illness and schizotypal disorder to predict poor outcome (34). In an Indian study, 'mixed' subtype of OCD (presence of both obsessions and compulsions), and any Axis I lifetime comorbidity predicted worse outcome (35). In a French study, lack of insight was the best predictor of treatment resistance (32).

Various clinical predictors of treatment non-response are identified in treatment studies. Early onset (64-66), continuous course and a longer

duration of illness (67, 68), poor insight (64, 69, 70), presence of sexual obsessions and washing compulsions (66), and hoarding (71) have been associated with poor response to SRI treatment. Comorbid disorders such as chronic tic disorder (72, 73), depression (66), schizotypal (34, 74), borderline, avoidant, paranoid (75) and obsessive-compulsive personality disorders (76) have also been associated with poor treatment response. Depression predicted poor treatment response in some (31, 66, 77), but not in other studies (78, 79).

Many demographic and clinical characteristics such as age, gender, age at onset, marital status, severity, and duration of illness are not predictive or consistently predictive of outcome in patients receiving CBT (51, 80-85). However, schizotypal personality disorder is predictive of poor response to CBT (86). Positive CBT response is associated with good motivation (87). Depression is also inconsistently associated with response to CBT (87-90).

It is evident that there are no consistent predictors of treatment response in OCD. It appears that early age-at-onset, long duration of illness, poor insight, mixed subtype of OCD, hoarding, presence of tic disorder and personality disorders (schizotypal personality disorder, in particular) are predictive of poor treatment response.

Conclusions and Future Directions

OCD is a common mental illness for which effective treatments are widely available but the data on long-term course and outcome is still limited. It is generally considered a chronic illness of waxing and waning severity of symptoms without full recovery. Some studies even suggest that SRIs and CBT may improve the clinical status but only very few patients actually remit completely (23, 31, 34). The evidence from some of the recent follow-up

studies suggest more optimistic outcome (28, 32, 35). For example in the Indian study, more than half the sample was in full remission (35). Optimistic findings of these studies, is substantiated, strangely enough by the findings of older studies when effective treatments were not available. In the review of older studies, Goodwin (22) observed that most outpatients had excellent prognosis whereas inpatients because of their chronicity, had poor prognosis. The subjects in the Indian study were largely self-referred, drug-naïve outpatients, the type of patients that are usually seen in general psychiatric settings than in specialized centers. It is possible that patients in the specialized centers and tertiary care centers are chronically and severely ill with high rates of comorbidity and treatment resistance. Therefore, it may not be possible to generalize the findings of such studies to a majority of OCD patients. Generalization of findings from such studies may lead to offering a pessimistic view of the course of illness to patients. It is also possible that currently available effective treatments have a positive impact on the short-term course of OCD, whereas the long-term outcome may not be significantly influenced. In other words, overall good prognosis observed in followup studies of longer durations could well be the natural course of the disorder that tend to remit substantially over many years. This is considered in view of positive outcome in older studies when effective treatments were not available. It is therefore important to examine the impact of SRIs and CBT on both short-term and long-term outcome of OCD.

Highly varying rates of outcome across studies is perhaps influenced by several factors such as symptom profile, insight, age-at-onset, severity and chronicity of illness, presence of comorbid Axis I and II disorders and varying duration of follow-up. Future follow-up studies would do well to consider

these variables in designing the studies so that it is possible to produce replicable results. There is limited data on the long-term efficacy of individual treatment options and their combination. Future studies will have to examine the effect of individual treatments and their combination on the long-term outcome in controlled studies involving larger representative samples of OCD patients. There is some suggestion from the sertraline and fluoxetine discontinuation studies that the relapse rates may be lower if SRIs are administered for a longer duration. To an extent, this is supported by the findings of Indian study where a majority of patients was treated with drugs for nearly 2 years and those in remission at the follow-up were off drugs for many years.

To conclude the prognosis of OCD may not be as bleak as is being widely portrayed. Poor prognosis in many studies may well have been due to inclusion of severely and chronically ill patients. There is, therefore, an urgent need to examine the long-term course and outcome of OCD in larger representative samples of patients treated with effective treatment options.

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Chapter 9

Management of Treatment-Resistant Obsessive-Compulsive Disorder

Sumant Khanna and Ravi Philip Rajkumar

Introduction

In the past two decades, obsessive-compulsive disorder (OCD) has been recognized as a common psychiatric condition with a prevalence of 1-3% in the community, a rate that has remained fairly constant across nations and cultures (1-6). OCD tends to run a chronic, waxing and waning course in a significant proportion of patients. It is one of the leading causes of psychiatric morbidity and disability (7), and patients with untreated OCD may have impairments in social functioning and quality of life comparable to patients with schizophrenia (8) and worse than those with depression or opioid dependence (9).

OCD was initially thought to be unresponsive to treatment, but subsequently, a range of effective treatments has been developed, based on two major approaches. The first of these – the pharmacological approach – was based on the observation that the tricyclic drug clomipramine was effective in alleviating the symptoms of OCD (10-12). Clomipramine, unlike other tricyclic antidepressants, is a highly potent inhibitor of neuronal serotonin reuptake, and this led to the serotonin hypothesis of OCD, and the use of serotonin-specific antidepressants – serotonin reuptake inhibitors (SRIs) - as first-line medications for OCD. The second, the psychological, was

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based on learning models of OCD, and used the principles of habituation and extinction to develop the techniques of exposure and response prevention (ERP), which is now well established as a first-line treatment for OCD, with an efficacy comparable to that of SRIs (13-15). ERP has further been refined by the application of cognitive theories, which led to the development of cognitive therapy as an equally effective treatment mode (16-19).

However, a significant proportion of patients, around 40% to 60%, do not respond adequately to treatment with either SRIs or CBT, both in short-term trials and at long-term follow-up (20-22). These patients remain significantly ill and disabled, with serious psychosocial consequences and impaired quality of life for themselves and their caregivers. This has led to various attempts to improve response and outcome in this group. Though there is no single treatment that is effective in this diverse group of patients, there is evidence that certain approaches may be helpful. This article aims to review these treatments, and provide guidelines for their use in clinical practice.

Definition and Assessment of Treatment Resistance

Definitions of treatment resistance

The study of treatment-resistant OCD has been hampered by inconsistencies in defining treatment resistance. Various closely related and overlapping terms – 'treatment-resistant', 'treatment-refractory' and 'non-responder' (20, 23) – are used to refer to these patients. The two instruments widely used for assessing treatment response are the Yale-Brown Obsessive-Compulsive Symptom Severity Scale (Y-BOCS) (24, 25) and the Clinical Global Impression – Severity and Improvement scales (CGI-S and CGI-I) (26). Most trials of acute-phase treatment in OCD have defined response as a

decrease of more than 25% (27) or 35% (28, 29) of the Y-BOCS score from baseline. Some authors (30, 31) suggest that the CGI may be a more sensitive instrument, and have proposed using a CGI-I score of 1 ('very much improved') or 2 ('much improved') as the criterion for response. Drug trials in patients with resistant OCD have used similar criteria, with some authors specifying an additional cut-off value for the post-treatment Y-BOCS score (for example, a Y-BOCS total score of 16) (32, 33). These studies have generally defined 'treatment resistance' as failure to respond to one adequate SRI trial.

Pallanti et al (20, 23) have reviewed the concept of resistant OCD, and provided operational definitions for terms such as 'response', 'recovery', 'remission', 'relapse' and 'refractory' in OCD, as well as a schema for defining various levels of treatment resistance similar to that developed by Thase and Rush (34) for resistant depression. 'Non-response' is defined as less than 25% reduction in the Y-BOCS score, and a CGI-I of 4 ('no change') or more. 'Refractory' OCD is defined as failure to respond to *all* available treatments. The complete staging system, comprising of ten stages ranging from failure of one SRI trial to failure of all treatment options, is explained at length in the original article (20).

However, the staging system they propose is cumbersome, and the rigorous definition of 'refractory' OCD they suggest may be difficult to use for either clinical or research purposes. Shetti et al (30) provided a more parsimonious definition of treatment non-response. In their study of the predictors of non-response in OCD, they defined 'non-responders' as patients who failed to show a CGI-I score of 1 or 2 after 2 adequate trials of SRIs. Hollander et al (35)

have referred to such patients as being 'treatment-refractory'. In this article, management strategies in patients who fail to respond to an initial SSRI trial as well as those not responding to multiple trials is discussed

Assessment of treatment resistance

When dealing with patients suspected of being treatment-resistant, it is important to exclude those who have failed to respond because of under-treatment. This phenomenon has been referred in OCD research as 'pseudoresistance' (36). Pseudoresistance may be due to a variety of factors including inadequate dosage, inadequate duration of a treatment trial, non-adherence to treatment, or inappropriate treatment. Optimum dosages for various SRIs, are listed in Table 1 (12, 37-42).

Furthermore, an adequate trial of an SRI is defined as at least 10 to 12 weeks of treatment, since most controlled trials have shown that the best response usually occurs by this point, even though initial improvement may occur earlier

Table 1: Optimum Dose Ranges used in the Treatment of OCD

Drug	Dose range
Fluoxetine	40-80 mg/day
Sertraline	150-250 mg/day
Fluvoxamine	200-300 mg/day
Paroxetine	40-60 mg/day
Citalopram	40-60 mg/day
Escitalopram	10-20 mg/day
Clomipramine	150-225 mg/day

(21, 30). In addition, patients may not be adherent to prescribed doses, either due to adverse effects or a perceived lack of efficacy (21). These factors should be adequately addressed before a patient is labeled 'treatment-resistant' or 'refractory'.

Predictors of Non-response to Treatment in OCD

Various authors have tried to identify those factors that might differentiate treatment responders from non-responders. While certain findings have been consistent across studies, others were not consistently replicated. Table 2 summarizes possible predictors of treatment non-response obtained in various studies that have specifically examined this issue. For a more extensive discussion of this topic, the reader is advised to consult the chapter on 'Long-term course and outcome of obsessive-compulsive disorder' in this monograph.

Table 2: Predictors of Treatment Non-response

Early age at onset
Longer duration of OCD
Mixed subtype of OCD (i.e. presence of compulsions)
Presence of sexual obsessions
Presence of washing compulsions
Hoarding
Poor insight
Prior treatment with medications
Personality disorders, especially schizotypal disorder
Tic disorders

Therapeutic Approaches to Treatment-Resistant OCD

In their review of the management of resistant depression, Fleck and Horwath (43) have listed four approaches:

> Optimization: optimizing the dosage and duration of current treatment
>
> Switching: changing to another first-line treatment approach
>
> Augmentation: addition of a drug which is not a primary anti-depressant to the treatment regimen, to improve response
>
> Combination: combining first-line treatments. Combination differs from augmentation in the nature of the treatments that are combined. For example, the use of two concurrent SRIs (e.g. citalopram and clomipramine) or a combination of an SSRI and CBT would be termed 'combination', while the use of an SSRI and a drug from a different class (e.g. risperidone) would be termed augmentation

This list of approaches is heuristically useful in understanding and managing patients with treatment-resistant OCD. Patients who have received sub-optimal treatment – that is, those with 'pseudoresistance' as defined above – require optimization of treatment, in terms of dose, duration and adherence. In this chapter, we will concentrate on the management of 'resistant' or 'refractory' OCD with the approaches mentioned previously. We will also discuss the role of psychosurgery and deep brain stimulation in treating patients with refractory OCD. Finally, we will provide a summary of treatment recommendations, outlining the sequence in which these approaches can be used in resistant OCD.

Switching strategies

Switching from one SSRI to another

Reviews of resistant OCD recommend switching to another SSRI in the event of non-response to an initial SSRI trial (23, 35). Evidence for this is limited, and the few studies that examined predictors of non-response have found that prior drug treatment may predict a relatively poorer response to fluoxetine, venlafaxine and paroxetine (29, 44). However, expert consensus opinions, guidelines, and specialists in the area recommend switching to another SSRI as a potentially effective strategy which should be tried in all patients (45-47).

Switching from an SSRI to clomipramine

Clomipramine has consistently been found to be superior to other SSRIs in meta-analytical studies, both in adults (48-50) and in children and adolescents (51). This association remains strong even after controlling for potential confounding factors. Studies using direct comparison methods between clomipramine and newer drugs found that it was comparable in efficacy to fluvoxamine (52, 53), fluoxetine (54) and venlafaxine (55). However, in all these studies, clomipramine was associated with more adverse effects. This evidence suggests that switching to clomipramine is an efficacious treatment option in patients who do not respond to SSRIs, although side-effects may limit its use. Expert consensus guidelines vary in their recommendations; the NICE guidelines (46) state that clomipramine may have improved efficacy, but SSRIs have a more favourable side-effect profile. On the other hand, the American Psychiatric Association practice guidelines (47) recommend switching to clomipramine as one of the first-line strategies in patients not responding to their first trial of an SSRI. In our center, the usual practice is to

prescribe clomipramine in patients who have not responded to 2 adequate SSRI trials (56).

Another approach to using clomipramine in resistant or refractory OCD is to administer it intravenously. Case reports and open trials found preliminary evidence of efficacy (57-59). Later, a single placebo-controlled trial conducted in non-responders to oral clomipramine found that intravenous clomipramine, given as 14 consecutive infusions at doses of up to 250 mg/day, was associated with a response rate of 43% (60). Though this approach appears promising, it is associated with potential cardiac and neurological side effects, requires close monitoring and the intravenous preparation is not widely available.

Switching from an SSRI to venlafaxine

Venlafaxine is a newer antidepressant which inhibits the reuptake of both serotonin and norepinephrine. Although its mechanism of action resembles that of clomipramine, its side-effect profile is more benign. Comparison studies with paroxetine (44) and with clomipramine (55) showed that venlafaxine was equal, but not superior, in efficacy to either drug. An open trial found that venlafaxine was beneficial in 76 % (22 of 29) of non-responders to SSRI treatment, with the mean dose of venlafaxine being 232.2 mg/day (61). However, in a switch study, venlafaxine was not useful in those who had not responded to paroxetine (62). The results of these two studies need to be viewed with caution in view of small sample sizes and open label design of the studies. Venlafaxine may be a useful option in patients who have not responded to SSRIs and clomipramine but it needs to be kept in mind that evidence is sparse (63).

Augmentation strategies

A variety of augmentation strategies have been used in treating OCD but only a few of them have been shown to be consistently useful. Table 3 summarizes the evidence base for available augmentation agents in OCD.

Of the augmenting strategies, the best evidence base is available for risperidone and it should be the first drug of choice for augmentation. Acceptable alternatives include haloperidol, olanzapine, clonazepam and quetiapine, while the other options mentioned show promise, but need to be investigated further. Nicotine, carbamazapine, lamotrigine, gabapentin, reboxetine, psychostimulants and N-acetyl cysteine have also been tried but there is insufficient evidence to recommend their routine use. Drugs such as lithium carbonate, buspirone, fenfluramine, inositol, thyroid hormone, older noradrenergic antidepressants and L-tryptophan have all shown to be ineffective in treating OCD (56, 84). These are probably best avoided, unless required to treat comorbid conditions – for example, lithium and lamotrigine for bipolar disorder.

Most augmentation trials are short-term trials, lasting a maximum of 8 weeks. If an augmenting agent has not produced the desired response by 6-8 weeks, it is preferable to discontinue it and proceed to another treatment approach. It is not certain how long augmentation should be continued once a patient has responded. However, a single trial of quetiapine suggests that once patients respond to the drug, their response is likely to be sustained for up to 6 months (85). In addition, a discontinuation trial has shown that, if antipsychotic augmentation is discontinued, over 83% of patients develop a relapse of OC symptoms, with most relapses occurring in the first 2 months (86). Maina et al (36), reviewing the same data, have suggested that

Table 3: Augmenting Agents in OCD

Drug class Antipsychotics	Evidence base	Dose range	Other comments
1. Risperidone (33, 64-66)	3 RCTs + open trials	0.5-4 mg/day (mean 2.2 ± 0.7 mg/day)	The best studied agent. 50% response rate; well tolerated except mild sedation; useful in adolescents .
2. Olanzapine (67-70)	2 RCT (one negative) + open trials	5-10 mg/day	46% response rate; can cause sedation and weight gain. An open trial suggests efficacy in refractory OCD
3. Quetiapine (71-73)	Negative RCT + positive open trials	50-400 mg/day (mean 112.5 mg/day)	61% response in open trial, only 27% in RCT (equal to placebo); may be useful in post-partum OCD
4. Other atypicals	Open trials, case series and case reports	Not defined	Open-label evidence for amisulpride and aripiprazole
5. Haloperidol (32, 74)	2 RCTs + open trials	2.5-10 mg/day (mean 6.2 ± 3.0 mg/day)	The most effective typical. May be most effective in those with comorbid tic disorder. Poorly tolerated by some patients
Clonazepam (75)	1 RCT + open trials	0.5-6 mg/day	Effective and well tolerated. A single case report of efficacy in refractory OCD
Glutamatergic agents			
1. Riluzole (76)	Open trial	50 mg bid	39% response rate, 54% improved. Well tolerated. Cost and availability are limiting factors
2. Topiramate (77, 78)	Case series and reports	150-250 mg/day	May not be well tolerated due to sedation and cognitive deficits; requires further study
3. Memantine(79, 80)	Case reports	20 mg/day	Effective in 2 of 3 published cases; needs further study
Miscellaneous agents			
1. Pindolol (81, 82)	Two positive RCTs	2.5 mg tid	The latest trial suggests effectiveness in 'refractory' OCD
2. Oral morphine (83)	Single double-blind trial	Flexible dosing	30% response in 'refractory' OCD (patients had failed 2-6 SRI trials); concerns about abuse and dependence

RCT, randomized controlled trial
SRI, serotonin reuptake inhibitor

augmentation treatment be continued for as long as SRI treatment in order to prevent relapse. If augmentation agents are to be tapered, this should be done slowly and under supervision, to detect relapses as early as possible.

Combination strategies

SSRI and clomipramine

Two case series and a randomized open trial have studied the efficacy of adding clomipramine to ongoing SSRI treatment in patients who fail to respond to monotherapy. In the case series, clomipramine at low doses (25-50 mg/day), when added to ongoing treatment with fluoxetine (87) or other SSRIs (88) was found to be effective. Pallanti et al (89) conducted a slightly more rigorous study. They selected 16 adult OCD patients who had not responded to clomipramine and fluoxetine monotherapies and randomized them to treatment with citalopram alone, or a combination of clomipramine and citalopram. While all 9 patients on combination therapy responded, only 1 of 7 treated with citalopram was classified as a responder. Though the small sample size and open methodology are important limitations, this trial suggests that clomipramine augmentation may be superior to switching in patients who have failed 2 prior medication trials. When using combination therapy, care must be taken to avoid precipitating the serotonin syndrome (90), and doses should be titrated carefully with appropriate monitoring.

SSRI/SRI and behavior therapy

If successive SSRI/SRI trials fail to produce improvement, the obvious next best choice is CBT. This does not mean that CBT is recommended only when drug therapies fail. It must be emphasized here that CBT is as much a first-line option as SSRIs, particularly in mild to moderate OCD. The expert

consensus guidelines recommend CBT with or without drugs as the first option in those with mild and moderate OCD (45-47). CBT and SSRIs are of comparable efficacy in treating OCD (91). If facilities are available, many clinicians consider combining both the options since there is reason to believe that combination therapy may be more effective than either of them although the evidence is far from conclusive (92-94). This was well demonstrated in a recent study by Foa et al (31). In this multi-center, randomized controlled trials, patients were treated in four arms: placebo, clomipramine alone, ERP alone, and combination therapy with ERP and clomipramine. After 12 weeks, all active treatments were superior to placebo, but both ERP alone (62%) and combination therapy (70%) had significantly greater response rates than clomipramine monotherapy (42%). The ERP and combination groups did not differ significantly, suggesting that the addition of medication did not significantly improve response rates to CBT.

Combined therapy may be superior to medication alone in medication non-responders (95, 96). CBT is also useful as an add-on treatment in patients who respond partly to medication (97). A multicenter study suggests that the combination of medication with CBT may yield a higher response rate, and decrease obsessions more effectively, than CBT alone (98). CBT has been shown to have sustained efficacy – even up to 5 years - when used in combination with SSRIs (99). A parallel-group study, in which patients received CBT and SSRI sequentially in different orders (100), concluded that CBT had a more specific anti-obsessional effect than medication, but that combined therapy produced the best improvement in mood. It appears wise to choose combined therapy as a first-line approach in patients who respond inadequately to either form of monotherapy.

Other strategies

Intensive residential therapy

Intensive residential treatment (IRT) involves in-patient or day-care therapy by a multidisciplinary team, and includes pharmacotherapy, daily CBT (2-4 hours) and group therapy delivered by therapists experienced in handling OCD. IRT was specifically developed for the management of treatment-refractory OCD patients, and has been shown to be a promising treatment option (101-103). The recent study from a specialized IRT unit in Massachusetts, which used the Y-BOCS as one of its outcome measures, found that IRT, administered over a period of up to 3 months, produced a mean fall in Y-BOCS scores of 30 % in a largely treatment-refractory sample (103). Notably, they found comparable falls in obsessions and compulsions scores, which was in contrast to earlier reports that behavior therapy was less effective for obsessions than compulsions (104). Predictors of good response to IRT in this study included female gender, better psychosocial adjustment, lower baseline OCD severity, and the absence of tic disorders (105). Where available, IRT appears to be a safe, well-tolerated and efficacious treatment, and should be considered in patients where other strategies have failed. However, the expertise required for successful IRT may not be readily available in all centers, which limits the applicability of this recommendation.

Family therapy

In a review of family-based approaches to OCD, Steketee and Van Noppen (106) point out that family factors often play an important role in the management of this condition. Expressed emotions (EE) from caregivers and family accommodation to compulsive rituals may have a negative impact on treatment outcome, while families can be involved in the therapeutic process

as co-therapists. The authors point out that none of the literature in this area has evaluated treatment outcome in a standard manner, but that available evidence suggests the efficacy of behavioral and group-oriented family approaches. They conclude that this treatment modality may be effective in treatment-refractory patients who have not improved on 'standard' forms of treatment. However, in the absence of well-designed and controlled trials, further research is needed to substantiate this conclusion. Where EE or family accommodation plays a role, they should certainly be addressed as they may impede response to other treatments.

High-dose SSRI therapy

It is possible that certain patients may show response at doses higher than the usual doses employed in treating OCD. A recent multi-center, double-blind study found that the use of high-dose sertraline (250-400 mg/day) for a period of 12 weeks was more effective than continuation therapy (200 mg/day) in patients who did not respond to an initial trial of sertraline (107). However, though the high-dose group showed greater symptomatic improvement, the number of responders, defined here as those having a 25% or greater fall in Y-BOCS scores, was not significantly higher. The higher doses were well tolerated by subjects in this study. A single case report (108) suggests that this approach may also be effective with citalopram. Though this approach may be beneficial in certain patients, we do not yet know who is likely to respond to this strategy, and it is best-considered in select patients in specialized centers.

Monotherapy with drugs other than SSRIs

Though SRIs are universally accepted as first-line pharmacotherapy in OCD, other drugs – predominantly those with a putative serotonergic

mechanism, such as clonazepam (109) and phenelzine (110) - have also been examined as stand-alone treatments. However, the only drug that has shown preliminary evidence of efficacy is the novel antidepressant mirtazapine. In an open-label study, 53.3% (16 of 30) of patients were responders to a 12-week trial of mirtazapine, given at a dose of 30-60 mg/day as tolerated (111). The continuation phase of this study involved randomization of these 16 patients to either mirtazapine or placebo for a further 8 weeks; the mirtazapine group continued to show improvement, while patients on placebo relapsed. Four patients in the open phase discontinued the drug due to side-effects. Though this approach appears promising, it is far from being conclusively established, and its applicability in treatment-resistant patients remains to be tested. Nevertheless, mirtazapine warrants further study to establish its role in the array of therapeutic options for OCD.

Psychosurgery

Though surgical approaches to the treatment of psychiatric disorders have been in use for over half a century, they were initially discredited due to their indiscriminate application and unacceptable adverse effect profiles, as well as the emergence of safer treatment approaches and ethical considerations regarding such surgery in the mentally ill. Of late, however, a growing body of literature attests to the fact that modern surgical techniques, when selectively and judiciously applied to patients with intractable OCD, may be both safe and effective (112-114). Newer surgical procedures are based on stereotactic techniques. Various groups in treating refractory OCD have used four specific procedures: anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leukotomy. Of late, gamma knife capsulotomy has emerged as a safer and non-invasive alternative to open procedures. Patient

selection criteria for these procedures have been much more stringent than in the past, and have usually included the following (112, 114):

1. Diagnosis of obsessive-compulsive disorder by standard criteria
2. Severe OCD, with objective evidence that the illness is causing significant suffering and marked impairment of psychosocial functioning.
3. Long-standing illness (usually more than 5 years)
4. Prior trials of all effective drug treatments. In practice, this means at least 3 serotonergic drugs (of which one should be clomipramine) and 2 augmenting agents, at adequate doses, for at least 12 weeks each.
5. An adequate trial of behavior therapy – usually a minimum of 20 hours is required.
6. Symptomatic improvement of less than 25% in the Y-BOCS following treatment.

Contraindications to psychosurgery in OCD include organic mental disorders, age below 18 or above 65 years, certain Axis I comorbid disorders such as psychosis and severe bipolar disorder, personality disorders (Cluster A and B disorders), substance use disorders, and the presence of brain pathology that would contraindicate surgery (112, 115).

Published studies of various procedures have found efficacy rates of 28% to 69% in various studies, with probably even more showing a partial response (113). Rates of symptom worsening range from 0-30%, though more recent studies report lower figures. Adverse effects following surgery include post-operative delirium, fatigue, weight gain, seizures, and headache; more serious but rare adverse effects include urinary incontinence (which may be

reversible), cognitive deficits, cerebral hemorrhage, personality changes of the frontal lobe type, and suicide – the latter in up to 3 % of patients.

By way of illustration, a recent published study used bilateral anterior cingulotomy, and found a response rate of 43% (6 of 14 patients), with no enduring cognitive or other deficits, though 3 patients reported transient and reversible memory impairment (115). Other adverse effects reported were transient symptom worsening, insomnia, weight gain and headache, none of which were severe or persistent beyond 3 months. Long-term outcome has also been examined, with response rates of 28% after 26 months (116) and 32% after 32 months (117) in patients who underwent cingulotomy. The latter study found partial improvement in a further 14% of subjects. The gains of psychosurgery for OCD are, therefore, probably sustained in the long run. Though a radical and even 'last-resort' measure, psychosurgery does appear to alleviate symptoms in a significant number of otherwise refractory patients with OCD, and should be considered in this subset of patients with resistant OCD (116). Of note is that all studies have continued medications and/or behavior therapy following surgery, which suggests that surgery, may not work alone, but in combination with other first-line treatment methods.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method of stimulating the cerebral cortex using a pulsed magnetic field, which is of potential use in the treatment of depression. Based on functional neuroimaging evidence of frontal hyperactivity in untreated OCD patients, rTMS to the right prefrontal cortex in patients with OCD was examined by Greenberg et al (118), who found that it significantly reduced symptoms in 12

OCD patients. However, out of three subsequent placebo-controlled trials (119-121), only one found evidence of efficacy (121). It is possible that rTMS may be effective in OCD, but larger studies are needed to answer this question definitively; this was the conclusion reached by a Cochrane database review (122). Its role in resistant OCD is currently unknown. However, given the safe and non-invasive nature of this treatment modality, a trial of rTMS may be warranted in patients who have failed more conventional treatments, before attempting more radical approaches such as deep brain stimulation or surgery.

Deep brain stimulation

The anatomical delineation of neural structures and networks involved in OCD has raised the possibility of using deep brain stimulation as a treatment for refractory OCD (123). Targets for DBS identified in OCD include the anterior capsule, the nucleus accumbens, the caudate nucleus and the subthalamic nucleus – though the latter site was 'incidentally' found to be effective in reducing OC symptoms in patients being treated for movement disorders. Evidence from case reports (124) and case series (125, 126) suggests that this approach may be beneficial in the acute phase in some, but not all patients; response rates were 66% in the first and 25% in the second study, and one patient in the latter committed suicide. DBS was otherwise well tolerated by subjects, though weight gain, nausea, diarrhea, and throbbing or tingling sensations have all been reported. DBS has obvious advantages over surgery in that it is potentially reversible, and that its benefits appear to be sustained in the long run, as was demonstrated in a 3-year follow up of 8 patients, where a response rate of 50% was noted (127). The latest study in this field examined 12 patients with treatment-refractory OCD, and found that 8 of them had a fall of 35% of greater on the Y-BOCS (128); these patients will be followed up

for a year, which will provide further information on long-term efficacy. However, there is a need to systematically examine the role of DBS in well-designed studies with adequate sample sizes and long follow-up periods. DBS requires specialized equipment and is not readily available in most centers. Moreover, it is inaccessible for a majority of patients because of its high cost.

Recommendations for the Management of Resistant OCD

From the above evidence, it is clear that there is no 'ideal' approach to the management of refractory OCD. However, using an evidence-based approach, the following recommendations can be made:

1. Non-responders to a single trial of medication should be treated, as a first-line approach, with either the addition of behavior therapy (combination therapy), or a switch to an alternate SSRI.
2. Non-responders to a trial of behavior therapy (ERP or CBT) should be treated with the addition of an SSRI (combination therapy) before trying other approaches
3. Patients not responding to two adequate SSRI trials should be treated either by combination therapy with ERP or CBT, by a switch to clomipramine, or by augmentation with risperidone (the preferred agent), olanzapine, haloperidol or clonazepam.
4. Patients not tolerating a switch to clomipramine may benefit from a switch to venlafaxine, or from the augmentation strategies mentioned above.
5. Patients not responding to a combination of behavior therapy and SSRI can be offered either a switch (to clomipramine, venlafaxine or another SRI) or augmentation as above.
6. Patients who have not responded to the above steps have essentially

failed all first-line treatments. If intensive residential treatment is available and feasible, it probably is the first choice at this stage. Alternately, second-line augmentation strategies (such as glutamatergic agents or pindolol) or combination therapy with clomipramine and SSRIs may be tried. High dose SSRI therapy, mirtazapine monotherapy and rTMS may also be considered at this stage although their efficacy in such refractory patients is unclear. Family intervention may be offered where family pathology appears to play a role in maintaining symptoms or causing relapses.

7. Patients who have failed more than two of the second-line treatments mentioned in Step 6 should be considered for more radical treatment approaches, namely deep brain stimulation or psychosurgery.

Conclusions

The management of treatment resistance is probably the single most challenging problem facing clinicians involved in the care of OCD patients. Though existing first-line treatments are effective, a substantial proportion of patients do not respond to them. For these patients, strategies based on combined therapy (medication and behavior therapy), switching from one drug to another (especially clomipramine) or augmentation are potential treatment options. A number of promising approaches exist for those not responding to these initial strategies, though further study is needed to clarify their relative roles. Finally, a small number of intractably ill patients may benefit from radical, yet effective modalities such as deep brain stimulation and psychosurgery. Further research into the predictors of response to various treatment modalities, as well as into the basic biology of OCD, is likely to yield fruitful new approaches to the management of this complex condition in the years to come.

Future directions for research

1. Though clomipramine's superiority over SSRIs has been established in meta-analyses, there is no direct evidence that it maintains this superiority with regard to resistant OCD. A large-scale, randomized controlled trial is needed to demonstrate whether clomipramine truly has an advantage over switching to other SSRIs in the management of these patients.
2. Preliminary evidence of the efficacy of venlafaxine is encouraging. Larger-scale, controlled studies on the use of venlafaxine in patients not responding to SSRIs are needed to delineate its role in this population.
3. Novel augmentation strategies, such as the glutamatergic agents, need to be explored further. Mirtazapine, which has already shown some promise as monotherapy, should also be examined as an augmenting agent.
4. Controlled trials of neurosurgery have not been possible so far, due to ethical concerns regarding placebo treatment. With the advent of gamma knife capsulotomy, performing sham procedures will be both ethically and practically feasible. This will allow researchers to conduct placebo-controlled trials of capsulotomy in intractable OCD. Similarly, controlled trials of deep brain stimulation are required.
5. Finally, newer insights into the neurobiology of OCD may pave the way for more fruitful treatment approaches. For example, a recent study has shown that mice in whom the SAPAP3 gene was knocked out exhibited self-injurious, grooming and anxiety-like behaviors

highly reminiscent of those seen in OCD. Reintroduction of the gene using a lentiviral vector reversed these symptoms, but fluoxetine treatment did not (129). The SAPAP gene encodes a protein involved in the targeting of receptors and signaling molecules to excitatory synapses, such as those utilizing glutamate. This provides further evidence that a paradigm shift away from the serotonin hypothesis of OCD is necessary, and that future treatment approaches may need to target entirely different molecules and pathways.

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Chapter 10

Role of Psychotherapy in the Treatment of Obsessive-Compulsive Disorder (OCD): Past Triumphs, Current Status and Future Directions

Paul M. Salkovskis

The first major breakthrough in psychological treatment for Obsessive-compulsive disorder (OCD) came in 1966 when Vic Meyer reported the successful treatment of two cases of chronic obsessional neurosis, using what he described as a treatment intended to modify patient expectancies of harm (1). A problem previously defined as untreatable was found to be open to modification. This treatment approach was the clear forerunner of the therapeutic approach we now know as Exposure and Response Prevention (ERP) and subsequent developments in cognitive-behavioural therapy (CBT). Meyer's rationale for treatment was derived from animal models of compulsive behaviour (see, for example Metzner (2), which proposed that ritualistic behaviours were a form of learned avoidance. Rachman et al, (3) developed and refined this type of treatment with exposure to feared situations whilst helping the patient to refrain from ritualising being central features.

Experimental support subsequently came from a series of experiments in which it was demonstrated that when a ritual is provoked discomfort and the urge to ritualise "spontaneously decay" when no ritualising takes place (4-6). In addition, it was also found that subsequent confrontation by obsessional

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stimuli without ritualising then resulted in progressively less discomfort being evoked, and the eventual extinction of obsessional fears. Rachman clearly set out the most influential form of the behavioural theory of OCD, which was based on Mowrer's two process theory: (7)

> Obsessions are previously neutral stimuli (intrusions) which have been associated with anxiety thought a process of *classical conditioning*
>
> Patients develop avoidance and escape responses; these responses terminate exposure to the feared stimulus. These behaviours are negatively reinforced, making them more likely to recur, through a process of *operant conditioning* (specifically, negative reinforcement)
>
> Termination of exposure prevents extinction of anxiety from occurring, thus maintaining both obsessional thinking and compulsive behaviours. (7)

Treatment based on this theory involves two elements

> Seeking to have the patient engage in prolonged exposure to the feared stimulus
>
> Identify and block any responses which terminate exposure to the feared stimulus

Together, these should ensure that extinction takes place as part of the treatment described as exposure and response prevention (8-13). Although easy to do, this treatment can be difficult to implement, and results fall well short of full remission of the disorder in all cases treated.

Cognitive-Behavioural Theory: Underpinning Current CBT Approaches

Cognitive theories and methods, based on the view that obsessional

thoughts are exaggerations of important aspects of normal cognitive functioning, were initially introduced as a way of dealing with the common problem that patients were too fearful to engage in ERP (14). Cognitive theories were then rapidly expanded into comprehensive accounts of OCD and how it might be treated (15-19).

The starting point for cognitive theories represented a shift of focus from the obsessional thoughts themselves onto the way these were interpreted (16). This dovetailed with existing behavioural approaches, as it emphasised the importance of negative meanings which motivate the development and maintenance of compulsive responses. Compulsions are not seen as primarily functioning to reduce anxiety, but rather as safety seeking behaviours (20) intended by the person to decrease the (perceived) likelihood of harm and the person's responsibility for it. Meaning therefore forms the "bridge" between the occurrence of intrusions and the triggering of overt or covert compulsive responses. The particular focus of interpretations relevant and/or specific to OCD has been the source of much debate (21).

Cognitive-behavioural theory thus proposes that people suffering from obsessions do so because they make particularly negative appraisals of intrusive thoughts, images, doubts and/or impulses. In particular, they interpret the occurrence and/or content of such intrusions as indicating that they are in some danger of bringing about harm to themselves or other people; that is, they believe that they are in danger of being responsible for such harm. A crucial aspect of this theory is that it is hypothesised that it is this perception of responsibility which results in obsessionals making efforts to "neutralise" intrusions and seeking to prevent the harm which is the focus of their

concerns. Responsibility appraisal thus generates both the attempts to neutralise intrusions and doubts, and the discomfort experienced following intrusions. (For more detailed accounts of this theory see 16, 17, 22, 23-28).

Responsibility is used in a specific way in the context of the cognitive-behavioural theory. The responsibility appraisal which is hypothesised as characterising obsessional problems is operationally defined as "The belief that one has power which is pivotal to bring about or prevent subjectively crucial negative outcomes. These outcomes may be actual, that is, having consequences in the real world, and/or at a moral level" (29)

The emphasis of this conceptualisation closely parallels the cognitive approach to other types of anxiety disorder in that a particular non-threatening situation becomes the focus of concern as a result of negative mis-interpretations of apparently innocuous stimuli; these interpretations are said to arise from particular beliefs concerning danger or threat. The way in which anxiety manifests therefore depends on the focus of threat perceptions and the emotional, behavioural and attentional consequences. The cognitive-behavioural theory regards intrusive thoughts, impulses, images and doubts as an integral part of normal everyday experience. However, when people develop a tendency to misinterpret their own mental activity as indicating personal "responsibility" it is predicted they will experience the pattern of discomfort and neutralising characteristic of obsessional problems. In those people where this tendency becomes relatively enduring, a full blown obsessional disorder will develop.

Maintenance Mechanisms

The interpretation of obsessional intrusions and doubts as indicating increased responsibility has a number of important and interlinked effects: (i) increased discomfort, anxiety and depression; (ii) increased focussed attention on these intrusions; (iii) greater accessibility of the original thought and other related ideas; (iv) active and usually counter-productive attempts to reduce the thoughts and decrease or discharge the responsibility which is perceived to be associated with them, including behavioural and cognitive "neutralising" responses. These may include compulsive behaviour, avoidance of situations related to the obsessional thought, seeking reassurance (having the effect of diluting or sharing responsibility) and attempts to get rid of or exclude the thought from the mind.

Each of these effects contributes to a worsening spiral of intrusive thoughts leading to maladaptive affective, cognitive and behavioural reactions. Intrusions interpreted as relevant to responsibility will therefore tend to persist and become the focus of further thought and action; irrelevant ideas can be considered but no further thought or action will ensue (25). In some instances, where a feared consequence is seen as imminent, behavioural responses can have the additional effect of preventing disconfirmation of the person's negative beliefs (29, 30). For example, a patient may believe that failing to wash his hands vigorously for 15 minutes could lead to severe illness in his family. Having washed in this way, none of his family become ill, providing him with evidence consistent with his initial belief, and leaving the belief intact (or even strengthening it) for subsequent occasions when the thought of contamination occurs again. Unlike other anxiety disorders (with the important exception of hypochondriasis; (30), the feared catastrophes are

more often seen as likely to occur at some distant time (e.g. family developing cancer, the patient going to hell after they die), and this makes disconfirmation difficult. Even in the washing example given above, the fear might be that infection in family members may be present but undetected for some months or even years before causing harm.

Appraisal of responsibility arising from the occurrence and content of intrusions can be at least partially independent, although often linked ("Having these thoughts means that I am a danger to my family"). This is not necessarily obvious in every instance; for example, a positive thought might be negatively appraised if it occurs incongruously on a sad occasion (e.g. an erotic thought at a funeral). When the meaning of the particular thought occurring is taken into account, however, the link between occurrence and content is usually evident.

In order to prevent the occurrence of intrusions and/or be aware of and limit the implications for responsibility, the obsessional patient often feels that it is necessary to pay close attention to his or her mental processes. For example, attempts to be sure of the accuracy of one's memory, to take account of all factors in one's decisions, to prevent the occurrence of unacceptable material, to ensure that an outcome has been achieved when the difference between achieving it and not achieving it is imperceptible (for example, deciding that one's hands are "properly" clean after washing in order to remove "contamination"). The choice of strategies is best understood from a safety seeking perspective; the patient will react in ways which he or she believes are most likely to be effective in reducing the threat of being responsible for avoidable harm. Safety seeking behaviours can thus be directed

at either preventing harm or preventing responsibility for harm. However, behaving in this way is likely to inflate the perception of responsibility further. This process seems to be like the common inference that "I'm running so there must be something very scary about this situation". The key belief may be that if one accepts that one can influence an event then one assumes responsibility for the possible outcomes. That is, by acting to reduce one's responsibility, one implicitly accepts the implication of being responsible in the first place. The short term "evasion" or transfer of responsibility therefore has the additional unwanted effect of strengthening more enduring beliefs concerning the extent to which one is responsible overall.

A further complication presented by a number of safety seeking strategies is that, by their nature, they appear to produce directly counter-productive effects. The person who "stares harder and harder at the switch" to make themselves "totally believe that it is off", for instance, usually experiences a degree of dissociation due to their fixed concentration on one unmoving point whilst at the same time closely monitoring mental processes (being sure that it is off), and this feeling of unreality is the precise opposite of the sureness which they explicitly seek. Generally speaking, OCD sufferers place more emphasis on internally referenced criteria, such as "feeling sure", "remembering clearly" and "it feeling just right" relative to externally referenced criteria like "the dirt had gone", than did the non-obsessional neutralisers (31). Conscious and deliberate efforts to feel extra sure or remember extra clearly, however, tend to generate doubt as opposed to yielding certainty, as well as creating the implicit expectation for future occasions that substantial effort may be required before a satisfactory end state is reached.

Cognitive-Behavioural Treatment: not Just Exposure and Response Prevention.

Although it is structured and focussed, cognitive behaviour therapy should not, of course, be practised prescriptively. The broad aim of therapy is to allow the obsessional patient to identify their present beliefs about the problem (e.g."I am a danger to myself or others if I fail to act to prevent harm" and to help them consider a less threatening alternative (e.g. "I am worried about the possibility of being a danger to myself or others and therefore I attempt to cope by using counter-productive strategies").

The Therapeutic Context for Cognitive-Behavioural Therapy for OCD

As in all CBT, a particular type of therapeutic relationship is required, in which the therapist seeks to maximise the extent to which the patient feels understood and wishes to actively engage in changing how they react to their problem. The use of normalising is particularly important, in that the patient is helped to see that their reactions are not as unusual, strange or crazy as they had previously thought, but can be readily understood in terms of their own experience. This normalising and empathic approach can be particularly helpful in terms of restoring or boosting the sufferer's self-esteem, and in helping to engage them in the active exploration and modification of their problem.

Therapy sessions are routinely audio taped, and the patient given the tape to listen to as homework. Audiotapes are used for two main reasons. First, therapy sessions are relatively long, and the patient is likely to have problems recalling all that was discussed. Second, if therapy is well conducted the patient

will frequently become upset, because therapy focuses on eliciting and modifying negative beliefs and behaviours which are central to the patients' concerns. The emotion experienced can make it difficult for the patient to process fully what went on during the therapy session. Listening to the tape allows the person to fully assimilate what occurred in therapy, and to more fully benefit from the new ideas discussed and discovered in the session. Inn addition, some patients like to listen to the tape with family members or others as a way of involving them and helping them to understand how they might be able to support the person in the process of change.

Cognitive therapy is conducted as part of a process of "guided discovery", in which questioning and discussion are used to help the patient to understand the nature of their problem and the factors involved in its persistence. Guided discovery almost inevitably leads the patient to reach an understanding of the changes which they need to make in order to overcome their problems. This style often incorporates the use of metaphors, stories and analogies as a way of normalising the patient's experience. Treatment techniques can be broadly split into "discussion techniques" and "behavioural experiments". These two types of strategy are very closely linked, and are complementary. In discussion, the patient and therapist work on achieving a better understanding of the problem, considering evidence, past and present, for the patients key beliefs and interpretations. As such discussion proceeds as a process of guided discovery, it will become clear that information important to answering crucial questions is simply not available. At such points, the aim is to devise behavioural experiments which have the effect of providing information relevant to these questions. Sometimes, such experiments can fully answer key questions, as in experiments which provide the patient with disconfirmation

of their feared consequences (20, 32). On completion of the behavioural experiment, the focus returns to discussion. In this way, good cognitive therapy involves the interweaving of discussion and behavioural experiments

.

As described above, assessment and treatment have the aim of helping the person to consider and evaluate an alternative view of their situation, viz: "Maybe you are not dangerous, but are very **worried** about being dangerous". Much of the early part of therapy involves the explicit identification of the two contrasting views of the patient's problem together with a detailed exploration of the implications of each, sometimes referred to as Theory A / Theory B. The patient and therapist work together to construct and test a new, less threatening explanation of the patient's experience, and then to explicitly examine the validity of the contrasting accounts. The early part of therapy therefore seeks to pose a general question of the form "Which explains things best: that you are a child molester, or that you fear being a child molester?". From early in therapy, therapists make it clear that they do not expect patients simply to change their views as a result of discussions and the construction of an alternative explanation. "Don't trust me, test it out for yourself" is the explicit theme of therapy sessions subsequent to the therapist and patient agreeing on a possible, anxiety based alternative account of their problem.

Reaching a shared understanding therefore involves the identification of key distorted beliefs and the collaborative construction of a non-threatening alternative account of their obsessional experience and preoccupations. This alternative explanation is important because it allows the patient to consider and explicitly test beliefs about the nature of their problem. Such beliefs emphasise the role of an inflated sense of responsibility for harm (to

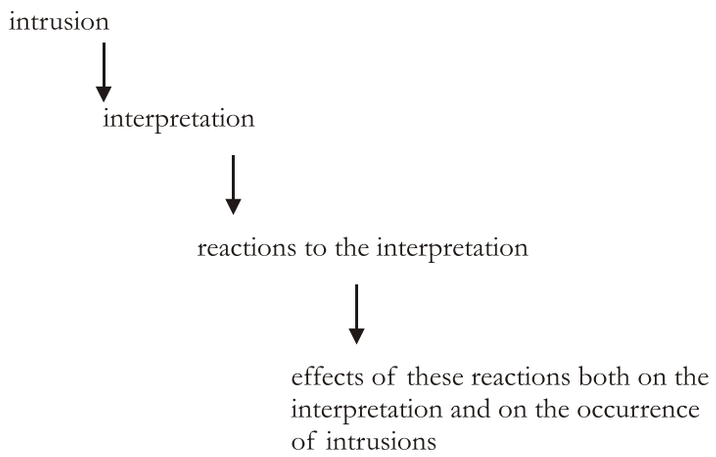
themselves and/or others) in generating and motivating compulsive and avoidant behaviours, and the way in which such neutralising and avoidant behaviour can in turn sustain or increase distorted beliefs concerning responsibility. One of the implications of such an approach is that it leads not only to verbal change strategies but also to a variant of exposure and response prevention in which belief change is the guiding principle; the two types of strategy, verbal and behavioural, are closely interwoven. That is, exposure and response prevention strategies are used as a way of helping the patient discover the way in which neutralising behaviour acts to maintain their beliefs and the associated discomfort, and that stopping such behaviours is beneficial. Discussion helps the patient understand how their problem works and directs them both to particular behavioural experiments and to ways of conducting these so as to maximise their understanding, which is consolidated in further discussion.

Cognitive Behavioural Therapy: The Main Stages of Treatment

Assessment

Assessment usually begins with a general clinical assessment including a brief history of the problem. In the more focussed aspect of the assessment, therapist and patient begin by identifying a recent episode during which the person's obsessional problem occurred or intensified. The context is primed (When was this? What were you doing at that time? What else was happening? How did you feel just before it began to be problematic?) Careful questioning and discussion about this episode is used to identify the particular intrusion (thought, image, impulse or doubt) and the significance that the person attached to it (i.e. the way the intrusion was interpreted/appraised). The therapist then helps the patient focus on the way their particular interpretation,

at the time in question, resulted in both distress and the desire (compulsion) to prevent or put right any possible harm which the patient has foreseen. Thus, discussion helps the patient and therapist identify the specific sequence of:



The focus then shifts to seeking an understanding the person's reactions to their interpretation of intrusions. It is particularly useful at this stage to help the person put these factors together in a formulation of the type depicted in figure 1 above. Again, questioning and discussion are the main techniques used. When the person believed that they may have harmed a passer by, how did that make them feel? When they became depressed and afraid, what effect did those emotions have on their thinking? What did they try to do? What was the effect of trying to push the intrusions out of their mind? Did seeking reassurance make them feel more or less sure? What about in the longer term? And so on. It is important to check whether this was a typical episode. If not, or if the patient believes that there are different types of episode, repeat the assessment with another specific episode, seeking to identify both commonalities and differences.

Home visits (or visits to places where the person is particularly troubled by their obsessional problem) can be a particularly useful adjunct to assessment, often helping the therapist to observe and work with the patient to explore the full scope of their problem.

Goal Setting

As the therapist gains a better understanding of the patients' problems, it is important to agree with the patient their principal goals. This can be divided into: Short term goals: goals which can reasonably be achieved in 2-4 sessions; Medium term goals: what can reasonably be achieved by the end of therapy and long terms goals: what the patient would like to do over the next few years. It is important to note that getting rid of all intrusive thoughts is not a helpful or achievable goal (because such thoughts are known to be both common and normal).

Beginning Treatment

A major aim of therapy is to explicitly help the patient to identify why they are distressed by their obsessional problem (because they believe that they are in danger of being responsible for harm). Treatment helps them to consider an alternative, altogether more benign explanation (that they are someone who is so sensitive to ideas of being responsible for harm that they take unnecessary precautions, which then have counter-productive effects). This comparison can be used in a "Theory A/Theory B" contrast. For example: "There are two ways of thinking about your problem. The first possibility is that your problem is that you are contaminated, and that you have to wash repeatedly because you believe that your failure to wash to your complete satisfaction could result in you being responsible for your family falling ill and possibly dying. The

alternative way of looking at it is that you are someone who, for understandable reasons, is sensitive to worries about being contaminated and who reacts to those worries in ways which tend to actually increase your concerns and which disrupt your life (for example, by washing excessively)".

Some patients will agree that the alternative makes sense of what is happening to them, and agree that this is the sensible way to work with their problems. Some patient will find this more difficult, initially suggesting that it is too difficult or dangerous for them to change their obsessional patterns of thinking and behaving. In such instances, it is helpful to contrast their previous counter-productive ways of coping with the possibility of change. The patient can be asked: "How much efforts have you put into dealing with the problem *as if* you were a danger to those around you?" Most patients are aware that this is the only way they have sought to deal with their obsessional concerns, so this is followed up with "How helpful has that been?". This discussion reaches the conclusion that any relief they have obtained from being obsessional has been short lived at best, and that trying to obsess one's way out of an obsession almost always results in a worsening of the problem.

This discussion is followed by further questioning which aims to have the patient consider the possibility for change and its likely consequences:

"Have you ever tried to deal with the problem *as if* it were a problem of excessive concern and worry?" Few, if any, patients have done this at all. The therapist suggests that, as the assessment indicates that this is now an obvious alternative way of dealing with their current problems, "Would you give it a wholehearted try for three months, then review it with me?"; assuming the answer is yes, it is then helpful to ask "How do you think it would be most

helpful to begin to change things?". This last question is a very helpful way of beginning things, as it usually results in the patient making active suggestions for changes in the way they respond to their intrusions.

Given that most obsessional problems reflect the patients' sensitivity to fears that they will cause or fail to prevent harm, it is not surprising that some patients express the concern that changing their behaviour as part of therapy might result in an over-reaction, so that they become excessively careless, dirty, and irreligious. If such fears are expressed, the therapist asks "In your experience, how easy is it to get less obsessional? How easy to get more obsessional?" Without exception, obsessional patients will indicate that it is all too easy to become more obsessional, and thus far has been extremely difficult to reduce their OCD. On the basis of this discussion, the therapist promises to help the person to become more obsessional in the unlikely event that, as treatment draws to an end, there have been unacceptable negative effects. That is, if some aspect of the changes they have made has resulted in a significant and, to the patient, undesirable reversal of their obsessional behaviour (that a cleaner has become dirty, that a checker has become careless). This has not so far been requested in the author's practise.

Changing the Way Intrusions are Interpreted by Normalising them

Given that the focus of treatment is on helping the patient to adopt and test an alternative, less threatening explanation of their problems, most therapy techniques focus on re-appraisal. A key component of this is normalising the experience of intrusions, helping the patient to change their understanding of the significance of the occurrence and content of intrusions. Some normalising will have taken place in the course of the assessment, through the

fact that the therapist is clearly aware of the type of intrusive thoughts which occur and the use of simple empathic statements (e.g. "So it's not surprising that you felt uncomfortable in that situation, because the thought 'I'll kill my baby' came to your mind just as you were cuddling him, and you thought that this might mean that you wanted to kill him". As treatment begins, the therapist uses more explicit normalising strategies, often beginning this phase by saying something like "people suffering from obsessions often wrongly believe that their thoughts are abnormal, insane or unusual. I'd like to examine whether that really is so." Guided discovery is used to help patients consider several important questions:

Who has obsessional thoughts? It is helpful to ask patients who are likely to be troubled by a intrusions concerning a range of obsessional themes, starting with some which they are not currently experiencing. Who is likely to be bothered by blasphemous obsessions? Obsessions of harming children? Violent obsessions? When might a positive thought be upsetting? The patient is asked to consider the effect of a thought about having a pleasant holiday on someone if it occurs in the context of a close friend being lowered into their grave. This discussion is used to emphasise the idea that it is not the intrusion itself which causes discomfort, but the way in which it is interpreted. By definition, negative interpretations are most likely in those who hold personal beliefs which are the opposite of the content of intrusions. Religious people are bothered and worried by blasphemous thoughts, gentle people by violent thoughts, and careful people by thoughts of carelessness. The discussion can also turn to consideration of the similarity between obsessional thoughts and worry. When people worry, what do they worry about? Do people worry more about good things not happening or terrible things happening? What does the

patient think the therapist might worry about? What intrusive thoughts might the therapist have? Once the patient concludes that obsessions usually concern areas in which one is particularly sensitive, the discussion re-focuses on their own obsessional intrusions.

How common are intrusive thoughts? Do they only occur in people suffering from OCD? Patients are invited to consider how common negative intrusive thoughts might be. Research findings indicating that almost everyone experiences unwanted and unacceptable intrusions are discussed (33, 34). Intrusions as a general phenomenon are discussed (including the fact that intrusions can be positive, negative and neutral intrusions). The patient is asked to consider what it would be like to never have intrusions; "Imagine that you had to plan every thought you were going to have; what would that be like?". The patient is asked whether intrusive thoughts might be useful. The discussion leads to the ideas that intrusions play an important role in problem solving and creativity. If one is seeking to problem solve, what's the best way to generate solutions? Should you only try to consider solutions which you think are good? The creative function of brainstorming is highlighted. When might violent thoughts be helpful? How about when one's family were being threatened? If someone were on the point of accidentally drinking something poisonous, might it be helpful to knock the cup from their hand as the quickest way of stopping them? This discussion might turn to consideration of how helpful or otherwise it might be to only have positive thoughts when someone directly threatens the patient or their family. The aim of this discussion is to conclude that intrusive thoughts are not only normal, but are also an important part of daily life.

Linking the Individual's History to the Formulation

People with a history of obsessive-compulsive disorder are likely to maintain a heightened sense of responsibility for events which may not be completely within their control. Sometimes there are very obvious links between the patient's early experience and their heightened sensitivity to responsibility. A more detailed assessment of the origins of such beliefs can be helpful as a way of challenging these ideas in the present, especially in cases where dysfunctional assumptions about responsibility are extremely difficult to change. For example, the patient can respond to a strongly held unconditional belief by reminding themselves that this is a product of "brainwashing". That is, beliefs which they learned from important authority figures as a child are returning and that they are responding to these as if they were still a child. An alternative is to challenge the idea from an adult perspective and consider whether these beliefs (a) were true then and (b) are still true now.

Understanding and Testing Counter-Productive Strategies

Having worked on de-catastrophising the occurrence and content of intrusions, the therapist then turns their attention to helping the patient understand and deal with responses which are involved in the maintenance of their negative beliefs. These factors fall into several broad categories, including selective attention and vigilance, the effects of mood (anxiety and depression), physiological arousal, neutralising behaviours and other counter-productive safety seeking strategies (including overt avoidance, thought suppression and cognitive avoidance, reassurance seeking, the use of inappropriate criteria for stopping a behaviour and so on). Much of this part of therapy focuses on those responses to intrusive thoughts, impulses, images and doubts which the

patient actively engages in as part of their safety seeking efforts. Such efforts are, of course, usually directed at attempts to ensure that harm does not come to themselves or others, and that they can be sure that they are not responsible (or risking being responsible) for such harm.

It is particularly important that the patient be helped to understand the impact of counter productive strategies. Several metaphors are clinically helpful here, including that idea that these activities (such as thought suppression and ritualising) are rather like digging to get out of a hole, trying to put out a fire with gasoline. That is, the action that one believes is making things better is actually making them worse. The patient is helped to question whether obsessional behaviour is a good way of dealing with an obsessional problem, or whether the things the person is doing as part of their "solution" to obsessional worries have in fact become a major part of the problem and its maintenance. For some, patients the discussion of the history of the development of their problem helps them to understand that, in the past, the harder they have tried to check, wash or otherwise neutralise, the worse their problem has become. It is suggested that it may not be appropriate to try to get out of a hole by digging faster or finding a bigger shovel. Another helpful strategy is to briefly describe the spontaneous decay experiments of Rachman and colleagues (4). The short term benefits of ritualising such as anxiety relief are contrasted with the longer term effects of obsessional fears, avoidance and behaviour. This discussion will inevitably lead to consideration of behavioural experiments involving elements of exposure and response prevention.

Consideration of the formulation leads to closely interwoven discussion and behavioural experiments designed to help the patient gather further

evidence for the way in which the mechanisms identified affect them. For example, the patient is asked to consider what usually happens to someone who tries to avoid thinking about something which is important to them. Have they themselves ever had the experience of trying not to think of something? Could they try now, in the office, not to think of giraffes. What happens? Why would trying not to think of something make this thing come to mind more both now and later? The discussion focuses on the fact that, if one wishes to avoid something, one has to keep in mind what is being avoided! Follow up homework experiments involving an alternating treatments single case experimental design can be helpful in gathering further evidence for the importance of the paradoxical effects of thought suppression. The patient keeps a daily diary of intrusive thoughts, also recording the amount of effort they put into suppression in the course of the day. They are then asked to try very hard to get rid of their intrusions by suppressing them on some days (for example, on Monday, Wednesday, Friday and Sunday), and to simply record the occurrence of thoughts without making any special attempts at suppression on the other days. The frequency of intrusions are graphed with the two types of days interspersed.

It is helpful to identify the way in which neutralising increases pre-occupation and anxiety in the longer term. Behavioural experiments can be used to systematically evaluate the effects of not neutralising as opposed to immediate neutralising. This is usually done in the context of having the patient make specific predictions about what will happen to factors such as their negative beliefs, degree of pre-occupation and doubt, discomfort and urge to neutralise if they do and do not neutralise (35, 36)

More on Behavioural Experiments

Behavioural experiments are used wherever possible to discover or demonstrate the effects of the patients' anxiety-based reactions to intrusions, with the basis for such experiments being drawn from discussion with the patient. Other examples include the use of mood induction procedures (37) if the patient does not understand the effects of negative mood on their thinking and beliefs. The negative impact of reassurance seeking and obsessional ritualising can be illustrated in similar ways. Discussion, in which the patient is reminded of the formulation previously identified, provides a detailed alternative account which highlights the way in which ritualistic behaviour is counter-productive in the long term even although it often feels beneficial in the short term (e.g. in helping the patient reduce their immediate discomfort). A helpful metaphor is to compare the obsessional problem to a playground bully. Again, questioning and guided discovery are the preferred mode of discussion. The bully may begin by making relatively small demands for money, and the victim feels relieved once they have bought them off. Does that mean that the victim is now free from any further threat? Why not? What happens next? How is that similar to the demands imposed by OCD? How can one break free of the demands of the bully? Will that feel comfortable at first? How will matters progress? The discussion aims to have the patient conclude that they need to take the offensive against their obsessional problems, challenging their beliefs rather than seeking to be safe from them. Again, the use of behavioural experiments to demonstrate the effects of reassurance seeking or ritualising is a helpful development from that discussion. Once the person is, in their heart, convinced that obsessional ritualising is maintaining and/or increasing their problems, systematic and self-initiated response prevention follows naturally. Often such a course of action is suggested by the patient themselves.

Challenging Responsibility Appraisals

The assessment, formulation, discussion and behavioural experiments described above will all tend to reveal beliefs focussed on an inflated sense of responsibility for harm. Such beliefs are crucial as they motivate the patient's efforts to neutralise, check that they have not caused harm or to undo any harm which they may have triggered. Clearly, because the patient understands the role of such beliefs in their OCD, whilst helpful, will not necessarily result in them being able to resist the urge to neutralise.

Often, more direct responsibility modification strategies are needed. One of the most helpful of these is the pie chart, in which therapist and patient work together to learn a strategy to deal with one of the commonest assumptions found in obsessional problems. This is a type of 'all or nothing' thinking, summarised by "if one can in any way influence a harmful outcome, then one is responsible for it". Such distortions are particularly difficult to deal with if they concern past events where, with hindsight, it is remotely possible that the patient could have prevented the negative event from happening. The fact that such prevention would have required foresight and unusual reactions to mundane situations is not usually regarded as in any way helpful by the patient. The pie-chart is used as a way of tackling all or nothing thinking whilst at the same time allowing the therapist to avoid debating the intrusion and thereby buying into the patient's attempt to neutralise and seek reassurance

.

The therapist draws a pie-chart which represents responsibility for the negative event in question. The patient is then asked to draw up a list of all possible influenced contributing to such responsibility, starting with their own actions or failure to act. All other influences are then listed, with as much time

as necessary being taken in order to ensure a thorough list. Once this is completed, the patient is asked to assign proportions of the responsibility to each factor in turn, starting at the bottom of the list. This means, of course, that the patient's own contribution is the last one dealt with. Note that the therapist does not seek to reassure the patient; the elements in the list come from the patient, with occasional prompting from the therapist, whose main job is to provide the structure in this discussion. Note also that the aim is not to convince the patient that they are not responsible, but rather to draw their attention to the fact that responsibility is multifaceted and characterised by shades of gray rather than black and white. Note also that such a strategy helps counteract the obsessional patients' tendency towards overlooking the role of those alternative explanations for which they do not have any responsibility. This exercise can also be helpful in making the point that it is seldom possible to prove that one had no influence whatsoever over a past event, and that reviewing such events in great detail will lead to an increase in doubt rather than to certainty that one was not responsible. A helpful way of providing a counterpoint to such a discussion is to ask the patient to consider whether they could, by a reversal of their obsessional behaviour, bring about the feared consequences. Could a washer assassinate someone by deliberately not washing their hands after going to the bathroom? Would not washing be a good way of committing murder?

Exposure Linked Behavioural Experiments

The techniques described above are all designed to help the patient reach the conclusion that they should cease their counter-productive strategies. As cognitive behaviour therapy progresses, the notion of exposure and response prevention becomes self evident, and a more planned and detailed

programme is initiated (13). Such a programme is discussed with the patient as the logical extension of the previous belief change strategies, with an appropriate combination of explicit aims; (i) to deal with compulsive/neutralising behaviours as a factor which is particularly important in the maintenance of their negative beliefs; (ii) as a way of demonstrating to themselves that the formulation is indeed correct, as it predicts that reducing neutralising will result in decreases both in anxiety and in negative beliefs; (iii) as a confrontation and disconfirmation of their negative expectancies where appropriate (i.e. to help the person to discover that their feared consequences do not occur when they stop their safety seeking behaviours when such disconfirmation is possible) (iv) to begin the process of regaining control over those aspects of their life which have come to be dominated by compulsive and neutralising behaviour, that is, to deal with compulsive behaviour as a problem rather than as a way of preventing harm. Exposure tasks are planned and set up with the explicit aim of bringing about such belief changes. Early on, therapist aided tasks are used to reveal and begin the process of challenging the negative appraisals activated by the person not neutralising. Discussions after the task is completed are used to consolidate and extend such belief change, particularly with respect to the patient's perception of the alternative account of their problems.

The importance of the patient assuming responsibility for their own actions (rather than simply complying with the suggestions made by the therapist) is emphasised. This is best achieved by the therapist modelling exposure exercises in the early stages, but rapidly moving to having the patient do things without modelling, then having the patient assume the role of identifying and planning exposure exercises themselves. Subsequently, the

patient is asked to plan and execute exposure tasks and to describe their responses without describing the task itself. Doing this removes the reassurance involved in having the therapist know about the details of the task undertaken by the patient. If the task is described, this serves as reassurance, as the patient believes that, had they undertaken something truly dangerous, then they therapist will react, making the absence of a reaction reassuring in itself. Note also that the rationale for the shift of responsibility to the patient is explained and reviewed in detail.

Direct or subtle reassurance seeking tends to occur in the course of therapy, most commonly without the patient being aware that "just mentioning" something they did as part of therapy to the therapist is problematic. To deal with this, the therapist first discusses the way that this works "When you mention things like that, are you interested in my reaction? Why is that?". In patients who find it hard to understand why such reassurance is not being offered, a simple discussion strategy can be helpful:

"You can have as much reassurance as you need. I'll cancel my remaining appointments for today, and we'll just work on reassurance. In turn, you have to promise me that the reassurance will last for the rest of the year". In this situation, the patient almost invariably points out that it is not possible, and on questioning will say that the effects of reassurance are only very temporary, often lasting only minutes. The therapist can then ask whether the patient believes that seeking reassurance is actually a helpful strategy. In this way, the patient tells the therapist that reassurance seeking is at best ineffective and at worst counter-productive and anxiety provoking. Again, this discussion is related back to the formulation.

More Re-appraisal and Belief Change Strategies

Other cognitive therapy techniques are used to help the patient to become more aware of the presence and role of threat and responsibility beliefs. These include modifications of the Dysfunctional Thought Record (38). The downward arrow and two column technique are used as appropriate in the context of particular issues arising in therapy (39, 40). The use of the downward arrow is tailored to the specific appraisals the person makes, which can be of the occurrence or the content of the intrusion, or both (41)

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Although the type of cognitive challenge strategies described here are specific to each patient, the outcomes of the challenge are always referred back to the person's individualised formulation. In OCD the therapist pays particular attention to the possibility that such techniques and their discussion with the therapist may become a form of subtle neutralising behaviour or may begin to take on characteristics of obsessional reassurance seeking.

Effectiveness of Cognitive-Behavioural Strategies

It is beyond the scope of this chapter to fully review the outcome data in OCD; the reader is directed to the comprehensive review which formed the basis of the clinical guidelines published by the UK's National Institute of Excellence (42). Cognitive behavioural therapy is identified there as the first line treatment of choice in both adult and childhood OCD. Cognitive treatment without the inclusion of exposure has been found to be at least as effective as behavioural treatment (43). Our own group has recently completed a comparison of cognitive-behaviour therapy as described above with behaviour therapy of equal credibility and duration based on an habituation rationale. Preliminary results of this unpublished trial show a clear

superiority of CBT over BT on all key measures both at the end of treatment and at one year follow up.

Future Directions: Clinical and Theoretical Issues to be Confronted

Those responsible for the provision of treatment for patients suffering from OCD are currently confronted by the necessity of providing good quality CBT, despite the very limited availability of competent therapists. The tension between biological and psychological understanding and treatment of OCD is not confined to the treatment arena. Although a variety of biological mechanisms have been proposed to account for obsessional problems, none have received consistent experimental validation. It has been suggested (39) that this problem at least in part arises from the type of theories of OCD currently used in biological psychiatry, which tend to rely on overly simplistic "lesion" or "biochemical imbalance" type models. Most commonly, there is a failure of such theories to account for the phenomenology of OCD; that is, there is little correspondence between the pattern of symptoms which patients report and the biological mechanisms which are supposed to account for them. By contrast, the main psychological theories adopt a continuum/normal processes type approach to OCD, explicitly specifying that there is no distinctive pathophysiology involved. However, even from such a normalising perspective it could be argued that identifying brain mechanisms involved in the key psychological processes, particularly in the way OCD relevant stimuli are processed, would have at least epistemological value. From such a perspective, it could be argued that a sensible (non-lesion based) neuroscience approach should take as its starting point an understanding of the psychological processes involved in OCD. The limited

success of pharmacotherapy and the extraordinarily high relapse rates suggests an important direction of such an approach. This type of approach would involve a "microanalysis", in which OCD is not seen as a "lump", but rather as a complex (but readily definable) interaction between cognitive processes and products. For example, it is possible to separately define the occurrence of intrusions, their vividness, the associated meaning, the strength of any urge to neutralise, the degree of resistance experienced, the intensity of any neutralising, and so on. The components of the model shown in Figure 1 can be characterised in terms of an assessment of at least thirty items. Based on such an approach, a microanalysis of the psychological changes associated with effective treatment with medication could be used to identify which components change in the course of successful treatment, and which revert to their original levels when medication is withdrawn and patients relapse. Such analyses should allow identification of a relatively smaller number of specific components of OCD which could usefully be dealt with following effective pharmacotherapy and should reduce relapse rates. By the same token, a comparable microanalysis should allow the identification of patients in whom the response to CBT has been less than complete, and who are likely to benefit from the addition of medication. Although complex to implement, the results of such a programme of research would inform both theoretical and clinical issues. Clearly, for such a programme to become a reality there is a need for some further elaboration of cognitive factors in OCD, although considerable progress has been made in this respect already. More problematic is the way in which biological theories have become both fragmented and have been built on the assumption that OCD must involve some fundamental disturbance of brain functioning. Paradoxically, then, helping biological researchers to achieve a more sophisticated view of OCD is probably the greatest challenge facing those working from a CBT perspective.

Prevention

As we develop a greater understanding of the nature and development of OCD, the clear implication is that this understanding may provide opportunities for prevention or "nipping it in the bud", that is, the development of primary or secondary prevention strategies. Quite what form this should take is unclear, but at this stage leading candidates would be to teach young people about the nature of intrusive thoughts and to learn to ignore them rather than to think of them as meaningful and occurrences to be "neutralised". Learning about the uncontrollability of intrusive thoughts, images and doubts and the controllability of responses to them, we may be able to prepare young people or people experiencing the first stages of OCD to deal with intrusions more effectively. If we can understand the kind of things which mark the transition from normal intrusive thoughts to obsessional disorders, we may be able to help and support them to deal with these situations, thereby reducing the likelihood of OCD developing. The clearest examples of triggers in the younger age groups include bullying, peer relationship problems and illness or death within the family. Previously held or newly developed beliefs (such as overly rigid moral codes, ideas about thought action fusion) are a further obvious target of preventative interventions (44).

More broadly, if we were to teach vulnerable individuals some of what they would learn in CBT (such as normalising of intrusions) and to use some of the techniques such as behavioural experiments to test out predictions about the way their thinking and behaviour impacts on the world, it may be possible to reduce the rate of people going on to develop different disorders. Historically, these questions are left unanswered as research of this kind is difficult to do. This is because the prevalence of OCD is around 1% and so in order to

determine whether prevention programmes have any real effect, sample sizes would need to be extremely large or risk predictions particularly strong.

Further Developing and Refining Treatment

Despite the success of CBT, many people suffering from OCD fail to make progress in treatment or have difficulty maintaining progress over the longer term. In order to improve treatment, we need to understand better what might define the problems experienced by those young people who do poorly in therapy. Rachman (45) describes how in some cases the individual does not improve because the treatment is inadequate or not adequately delivered, which he calls 'technical treatment failures'. This is a kind way of indicating that some therapists do not do treatment very well. In other cases, treatment may be delivered adequately but the individual makes limited progress and these are described as 'serious treatment failures'. Clearly identifying factors likely to result in relatively poorer outcomes will, in research terms, allow research to turn failure into success.

In clinical settings, there is often an assumption that many of the difficulties in treatment arise from secondary complications, such as poor motivation, and are down to the individual rather than the therapist. This can be seen as a type of self-serving cognitive bias on the part of the therapist. However, Stobie et al's (46) study suggested that it was technical failures that were extremely common and advocated specialist training and supervision for clinicians in CBT, as well as the development and use of quality assurance measures to ensure that individuals are actually receiving what they are being offered. It may be that some of these technical failures are related to difficulty with engagement and it is vital that clinicians are approachable, use the right

language, listen respectfully and adapt therapy appropriately according to the problems experienced by the person to be treated.

Little is currently known about why some people make little progress with adequate treatment, although co-morbidity and family factors may be involved. The idea that "one size fits all" in terms of therapy is, of course, risible. Research indicates that comorbidity (e.g. Axis II, "personality disorders" do not usually prevent therapeutic change with treatment when the main problem is an anxiety disorder. However, such patients tend to have more severe problems and, at the end of standardised treatment packages are more symptomatic that patients who do not show such comorbidity. Further treatment sessions typically result in further change and the achievement of similar end state.

The Provision and Dissemination of Treatment

Studies on OCD in adults suggest that it is typically many years after obsessional symptoms significantly interfere before a diagnosis is made (46, 47). With young people as in adults, presentation to clinical services tends to be rather late in the natural history of the problem if it happens at all. A range of factors can contribute to unwillingness to seek professional help, including fear of or shame about revealing what they are experiencing to others. Families can sometimes actively ignore symptoms, trying to reassure themselves and the sufferer that there is nothing wrong and resisting seeking treatment because of the concerns of what a diagnosis may bring in terms of stigma and blame. For professionals to reach a greater proportion of people who would benefit from treatment, we need to change the way mental health problems are perceived. The most obvious way of achieving this is likely to be through a

greater awareness of OCD and the effectiveness of treatment in both in educational and primary care settings. Strategies designed to reduce the stigma of mental health problems in general and OCD in particular are needed; careful media work and work with the anxiety disorder charities are promising in this respect.

Currently, guidelines from the National Institute of Clinical Excellence (NICE) for the treatment of OCD recommend a stepped care approach. This approach advocates beginning with the least expensive and intrusive interventions and moving on to more intensive treatment as and when necessary. In OCD, NICE suggests beginning with self-help for young people where the OCD is mild, but as yet there is no evidence base for this and self-help literature for young people with OCD is not generally available. There are risks associated with low-intensity treatments, in that a failure to respond could have a negative impact on the person's self-esteem and reduce their motivation to continue to try to change, discouraging them from seeking subsequent treatment. It may also undermine their response to further treatment or lead to them being seen as 'untreatable' by professionals if they have already received some version of CBT.

Conclusions

The psychological treatment of OCD has advanced greatly over the last decade from a state of stigmatising pessimism to heady optimism. There are many opportunities to extend our treatments to those who previously did not respond, for more effective and efficient treatment implementation, for disseminating effective treatments and perhaps even early intervention and even prevention. There seems now to be real possibility that, given the right

strategies and sufficient resources, we may be able to aim at changing the epidemiology of OCD.

The lessons learned over the past three decades lead to the conclusion that OCD can be cured. Not just improved, not "learning to live with the problem", but cured. The facts that it can at times be difficult, time consuming, incomplete, expensive and harrowing for all concerned do not detract from the simple observation that it can be done. This being so, the future needs to hold a new set of apparently achievable aspirations; these are, how to "cure" OCD earlier, more efficiently, in more people and more easily. It is also important to recognise we need to work out how to help those people who "partially respond". To achieve these goals, we need to achieve an even better understanding not only of factors involved in the origins and maintenance of OCD and the way in which it manifests, but also those which relate to the process of achieving and sustaining excellent treatment response.

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Chapter 11

Cognitive Behavior Therapy in Childhood OCD

Nitin Anand, Suresh Bada Math, Y C Janardhan Reddy and Shoba Srinath

Introduction

Though obsessive compulsive disorder (OCD) is a common psychiatric disorder in children and adolescents, it is often undiagnosed. In the absence of adequate treatment, OCD can prove to be severe and debilitating. It follows a chronic, waxing and waning course, frequently extending into adulthood for a majority of children. (1-7). OCD affects as many as 2-3% of children (8-10) with point prevalence rates of 0.5% and 1-3% in children and adolescents respectively (10).

Children suffering from OCD have disrupted development, difficulties in social interaction and interpersonal relationships, poor concentration levels and are typically academic underperformers (6, 11, 12). The rates of comorbid psychiatric disorders are high (70-90%) (2, 5, 13-15) with half of them having multiple comorbid conditions (13). Children suffering from OCD are at

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heightened risk to develop other clinically significant psychiatric disorders, seriously impacting the development of their personality (16). The most common comorbid disorders are depression (40-70%) (3, 5, 10, 16), attention deficit hyperactive disorder (30-50%) (16-18), oppositional defiant disorder (30-40%) (16), developmental disorders (speech & language) (20-25%) (14, 16) other anxiety disorders (30-70%) (3, 10, 16) and tic disorders (20- 40%) (5, 15, 16, 19).

A meta-analysis of twelve published, randomized, controlled medication trials in children reported only 30% to 40% reduction in OC symptoms with pharmacotherapy (20). Hence, there is a need to explore modalities of additional treatments. Cognitive-behavior therapy (CBT) involving exposure and response prevention is the psychotherapeutic treatment of choice in treating children with OCD. This is often recommended as the first line of treatment (21). CBT is recommended for treatment in children on the basis of its demonstrated efficacy in treating adults with OCD as well as the efficacy data collated from open label and randomized controlled trials in children. There is further demonstrable belief that OCD in children bears striking similarity to its manifestation in adults. Though meta-analyses have established CBT as a promising treatment for OCD in children and adolescents, the fact remains that it could demonstrate better outcomes when combined with medication; ahead of a standalone treatment. (22-25). The attempt here is to review the efficacy data briefly and address issues such as appropriateness of CBT in young children, role of family, role of insight, individual vs. group CBT, quality of CBT, factors predicting the outcome of CBT, role of CBT in SRI nonresponders and long term efficacy of CBT.

Efficacy of CBT in Childhood OCD

A review of the published literature on the efficacy of CBT in children with OCD reveals that a majority of the studies are either open label or case series (Table 1). There are only four randomized, controlled trials to evaluate the efficacy of CBT in children. Of these, the pediatric OCD treatment study (POTS) is the only study that is extensive and methodologically rigorous with respect to minimization of bias associated with design and implementation (26). The trial compared the efficacy of discrete treatments - CBT, sertraline, placebo against a combination of treatment of CBT and sertraline. POTS extended to include112 patients aged 7-17 years with a DSM-IV (27) diagnosis of OCD (CY-BOCS = 16) (28) over a period of twelve weeks. The outcome measure of clinical remission was predefined as change in CY-BOCS score $\leq$ 10, over a period of 12 weeks as rated by an independent evaluator, who was masked to treatment status. Ninety-seven of 112 patients (87%) completed the 12 weeks of treatment. The significant results that emerged from the study included (26):

Clear demonstration that all interventions were superior to placebo treatment

Combined group (CBT and medication) treatment was superior to CBT alone and sertraline alone

CBT alone scored higher in efficacy in comparison to sertraline alone

Four meta-analyses have been published examining the efficacy of CBT in pediatric OCD.(Table 2).A meta-analysis of 18 studies by Abramowitz et al. (22) reported that CBT produced larger effect sizes and greater rates of clinically significant improvement when compared to treatment with medication. Authors of the study have also cautioned about methodological

Table 1. Studies Assessing Efficacy of CBT in Childhood OCD

Study	Sample	Intervention	Results
Randomized control trials			
Barrett et al (44) [a]	77	Individual CBFT (24)	65% mean symptom reduction 82% diagnosis free at 3 months 65% diagnosis free at 6 months
		Group CBFT (29)	61% mean symptom reduction 76% diagnosis free at 3 months 87% diagnosis free at 6 months
		Waitlist (24)	No reduction in Symptoms
POTS study (26) [a c]	112	CBT (28).	39% excellent responders 46% mean symptom reduction
		SSRI (28)	21% excellent responders 30% mean symptom reduction
		CBT/SSRI (28)	54% excellent responders 53% mean symptom reduction
		Placebo (28)	4% were excellent responders 15% mean symptom reduction
Asbahr et al (57) [a]	40	GCBT (20) Sertraline (20)	Statistically significant reduction of symptoms at post treatment in both the groups. However, at 9 months follow up CBT group had significantly lower relapse rate in comparison to sertraline.
DeHaan et al (59) [a d]	22	BT (12)	60% mean symptom reduction 67% responders
		Clomipramine(10)	33% mean symptom reduction 50% responders
Open label trials			
Valderhaug et al (58) [a]	24	CBT	60% mean symptom reduction 68.8% mean symptom reduction at 6 months follow-up
Martin and Thienemann (54) [a]	14	Group CBT	24.76% mean symptom reduction at post treatment.
Himle et al (76) [a]	19	Group CBT	Statistically significant improvement at post treatment
Piacentini et al (63) [b]	42	CBT ± Medication	45% mean reduction in symptoms No difference between CBT alone or CBT +Medication. 79% significantly improved (CGI < 2)
Benazon et al (1) [a e]	16	CBT	48% mean symptom reduction 25% recovered

Study	Sample	Intervention	Results
Thienemann et al (56) [a]	18	CBT ± Medication	25% mean reduction in symptom severity
Fischer et al (80) [a]	15	CBT ± Medication	32% mean reduction in symptom severity 50% mean reduction in symptom severity at 6 month follow-up
Franklin et al (36) [a]	14	CBT ± Medication	67% mean symptom reduction Gains maintained at mean 9 months follow-up CBT alone as effective as CBT + Medication No difference-intensive Vs weekly sessions
Wever & Rey (81) [a]	57	CBT ± Medication	60% mean reduction in symptom severity 68% remission at post treatment 39% weaned off drug
March et al (43) [a]	15	CBT ± Medication + Anxiety management training	50% mean symptom reduction Gains maintained at mean 18 months follow-up Medication discontinuation in 6 patients with booster sessions
Bolton et al (82) (Multiple case reports)	15	ERP + Flooding + Operant procedures+ medications+ Family therapy	80% showed prominent improvement 50% maintained improvement at follow-up.

[a] CY-BOCS was used as a measure of severity of illness
[b] NIMHGOCS was used as a measure of severity of illness
[c] Excellent responders are defined as having a score of less than or equal to 10 on CY-BOCS
[d] Responders are defined having as 30% or more symptom reduction on CY-BOCS.
[e] Recovered status based on the reliable change index.

differences that existed between medication and CBT studies. This study, however, does not take into account the risk of bias in the studies and includes both controlled and uncontrolled studies. The Cochrane Database meta-analysis examined only four randomized-controlled studies involving 222 participants as part of the review (25). Authors concluded that CBT appeared to be a promising treatment for OCD in children and adolescents and that it can exhibit better results when administered in combination with medication rather than medication alone. However, there was no conclusive evidence to prove that CBT was superior to medications alone. The review also concluded

Table 2. Meta-analytic Reviews Assessing the Efficacy of CBT in Childhood OCD

Reviews	Type of studies	Sample size	Number of studies	Results
O' Kearney (24)	Randomized Control trials	262	5	CBT + Medication is more efficacious than medication alone, waitlist & placebo.
	Open label trials	300	14	CBT should be considered equivalent to medication & can provide better outcomes in combination with medication.
Freeman et al (23)	Randomized Control trials + Open label trials	231	12	CBT is a promising treatment Preliminary evidence indicates that individual and family based CBT trials appear to be effective. Results are confounded by concomitant medications.
O' Kearney et al (25)	Randomized Control trials	222	4	BT/CBT is effective. BT/CBT + Medication produce better outcomes than medication alone. Combination is not superior to CBT alone
Abramowitz et al (22)	Randomized Control trials + Open label trials	815	18	Medications and CBT, both are effective in reducing OCD symptoms. CBT produces greater rates of clinically significant improvement, in comparison to medication. ERP should be the first line treatment for childhood OCD.

that there was no basis to prefer medicines over CBT as the first line of treatment. A meta-analysis by the same group critically appraised the evidence surrounding the benefit of CBT for pediatric OCD from controlled and single group studies (24). Selected studies were categorized by study type and by risk of bias classification. The review concluded that efficacy of CBT and medications did not differ significantly. There was some evidence from the review that CBT combined with medication is significantly more efficacious than nonactive controls or medication alone but not relative to CBT alone. The findings of the Cochrane review (25) and that of O'Kearney et al (24) are largely substantiated by a recent meta-analysis (23).

Based on the results of four meta-analyses and the POTS study, it is appropriate to initiate both CBT and medication or to consider CBT alone as the first line of treatment. However, the authors of these meta-analyses have highlighted the limitations of the available CBT research literature:

no treatment studies have examined treatment of children with OCD below the age group of 7 years

most of the studies reporting the efficacy of CBT have included patients who were on medication resulting in a consequential dearth of studies examining the true effect of CBT

small sample size and varying study design, study comparability and study quality makes it difficult to compare the studies and generalize the findings to the entire pediatric group (23-25).

Is childhood OCD Different from Adult onset OCD?

CBT in children as it is practiced now is simply a downward extension of its application in adults. The premise here is that OCD in children is similar to its

manifestation in adults and therefore, the same strategies may work. Although OCD in children is similar in both prevalence and clinical characteristics to adult OCD, there are reasons to believe that the disorder has several distinctive features that may have implications for its management. A number of studies have questioned the developmental continuity between pediatric and adult OCD (19, 29). The onset of OCD has been recognized to have a bimodal peak. In children, the mean age of onset of OCD is reportedly between 7 years to 12 years, and another peak during early adulthood with mean age of onset between 16 years to 18years (5, 19, 29). Pediatric OCD is more common in boys (30), and is highly comorbid with disruptive behavior disorders (19, 31, 32) and tic disorders (15, 16). Children often perform compulsions in the absence of obsessions and children with tic disorders often report their rituals as being performed in response to an irresistible urge, an 'empty' feeling, or an otherwise vague sensation (the 'just right' phenomenon) (31, 33, 34). Moreover, children with comorbid tics many not have well-developed cognitions that trigger their compulsions. Children with OCD may be less likely to perceive their symptoms as nonsensical or ego-dystonic in nature (16, 31, 35). These unique features may influence the rationale of CBT and its implementation in children and adolescents with OCD.

Is Cognitive Behavior Therapy Appropriate for Very Young Children?

Available literature suggests that current CBT programs employed for children and adolescents are almost similar to adult treatment programs (36, 37). However, Piaget's theory of cognitive development postulates that abstract thinking develops during the phase of adolescence. Applying cognitive techniques in very young children may not be very effective given

that self reflection and abstract thinking are not well developed (25). A majority of the studies about CBT in children included the children above the age group of 7 years (23); therefore the applicability of CBT to very young children remains relatively untested. However, there are researchers who argue that children as young as 5 years can participate in cognitive tasks, including cognitive training (38). Case reports of successfully treating OCD in children of less than 6 years by utilizing CBT also exists (39-41). Hence, the issue correlating age and appropriateness of cognitive therapy continues to be a point of contention. The best available option is to use more of behavior techniques in younger children while administering a combination of cognitive and behavior techniques in older children and adolescents. There is clearly a need to further develop sensitive CBT programs catering to the needs of children of differing age groups.

Role of Family

Involvement of family members is central to the success of CBT in children and adolescents with OCD (42, 43). Along with individual sessions with the patient, focused family sessions with parents, towards involving them in CBT as cotherapists, play a crucial role in the treatment outcome. The effectiveness of participation by parents as cotherapists in treatment has been demonstrated in the treatment of children and adolescents with OCD (44). This is significant because family members in absence of awareness may unintentionally facilitate the rituals or compulsions (45). Families affect and are affected by OCD through their accommodation and participation in rituals (48-50). Alternatively, families could display high levels of expressed emotion and increased parental catastrophizing behavior (2, 51, 52). Despite the possible negative influence of family dysfunction on the long-term outcome

(53), there is very limited data on the role of family in the implementation of CBT (44, 54, 55). It is important to note that all the three studies have reported positive outcome with involvement of family in the therapy. Parental awareness about OCD and involving them in CBT can provide assistance in monitoring the symptoms and ensuring the compliance in homework assignments and ERP tasks. Parents can also be taught about differential reinforcement measures (37, 43, 46, 47).

Individual versus Group CBT

A randomized controlled study comparing the efficacy of (i) individual CBT; (ii) group CBT; and (iii) a waitlist control group in the treatment of seventy seven children and adolescents with OCD; reported that clinically significant change occurred in OCD diagnostic status and severity across both individual and group CBT, when compared to waitlist control group (44). However, there was no significant difference in improvement ratings between individual and group CBT. Treatment gains, which occurred during individual and group CBT, were maintained up to 6 months during which monitoring was maintained (44). An open label trial of manual-based group CBT treatment protocol in adolescents reported clinically significant improvement from baseline and documented that adolescents consistently shared information and designed exposure interventions for themselves and also for other children in the group. They also suggested that group CBT was palatable to adolescent patients in their study (56). Another study by Asbahr et al., (57) compared the efficacy of group CBT with administration of sertraline and reported that both the groups were similar in outcome at 12 weeks, but during a 9-month follow-up period, subjects in the group CBT had a significantly lower rate of symptom relapse. From the available evidence, it is clear that

group CBT is significantly similar to individual CBT in efficacy. This finding has particular relevance to clinical practice in developing countries like India, where individual therapy may not be feasible due to shortage of trained staff and requires further examination in larger samples.

CBT in Non-specialized Clinical Settings

Majority of pediatric OCD studies published are from tertiary care centers or from academic institutes, where specialized experts handle difficult cases that are usually referred to them. Findings from these studies cannot be generalized to pediatric OCD groups and nonacademic community child psychiatric settings. In an open label trial of manual-guided CBT in 28 children and adolescents with OCD from a nonacademic community child psychiatric setting, there was a mean symptom reduction from baseline on the CY-BOCS of 61% at post-treatment, 60% at the 3-month follow-up, and 69% at the 6-month follow-up stage, suggesting that the manual-guided CBT for childhood OCD can be successfully implemented. The improvement can be sustained in nonacademic community child psychiatric settings as well (58).

Structure of CBT

Meta-analytic research literature reveals that CBT interventions ranged between 12 and 20 sessions, with a session duration of 60 minutes to 90 minutes (24, 25). The total duration of therapy hours ranged from a minimum of 12 hours to a maximum of 30 hours and was spread over 12-20 weeks (26, 44, 59, 60). Sessions in all interventions programs were conducted on a weekly basis. From the available literature, it may be assumed that adequate therapy involves 15-20 sessions, with each session lasting for 60-90 minutes, while being spread over 16-20 weeks (37, 61).

On comparing the efficacy of intensive residential daily CBT program and an out-patient weekly basis CBT program, both programs were equally effective treatment approaches for pediatric OCD. Intensive treatment may have slight immediate advantages over weekly CBT, although both modalities have similar outcomes at the 3-month follow-up stage (62). Theoretically speaking, on one hand the therapist in an intensive residential program can observe and monitor the child on a daily basis; while on the other hand administering CBT on an outpatient weekly basis provides an opportunity to generalize the skills in the child's home environment. However, both the approaches have shown similar results at the 3-month follow-up stage. An interesting finding by Piacentini et al (63) revealed that the therapist experience did not have any impact on the treatment outcome of CBT in childhood OCD. Similarly, a review by Mataix-Cols and Marks on self-help interventions (like bibliotherapy, self-help groups, telecare and computer-aided self-help) for OCD, with minimal therapist contact, has found these to be promising in adults (64). This area requires further exploration in pediatric OCD, especially for patients in developing countries with characteristically minimal access to CBT.

Role of Insight

In childhood OCD, 35% to 40 % have poor insight into their symptoms (16, 35) and it has been argued that poor insight patients (both children and adults) have poor outcome on pharmacological and CBT treatment (65-68). This is possibly because poor insight patients may deny their symptoms, may not participate actively or comply with CBT treatment, hence showing minimal improvement. The therapist in these circumstances is required to be tolerant and innovative in designing and utilizing the behavioral principles of

reinforcement to facilitate ERP tasks. There are no systematic studies comparing poor insight with good insight as a predictor of outcome of CBT treatment in childhood OCD. A review by Piacentini suggests that along with CBT, adjunctive interventions including focused family intervention, anxiety management training, cognitive restructuring, contingency management, and supportive therapy may enhance the efficacy of ERP through the enhancement of treatment compliance and motivation (47).

Role of CBT in SRI Non-responder Childhood OCD

A meta-analysis of 12 published, randomized, controlled medication trials in children reported only 30% to 40% reduction in OC symptoms with pharmacotherapy (20). There is paucity of data regarding the efficacy of CBT in SRI nonresponder patients with pediatric OCD (56, 69). However, preliminary data from CBT in SSRI nonresponders in adults appears encouraging. CBT was found effective in two open label trials of patients who had undergone one adequate SSRI trial (70, 71). In an another open label trial of CBT in SSRI nonresponder adult OCD patients, those who had undergone at least two adequate trials of SSRI medication, reported a 39.5% mean decrease in YBOCS scores at the post-treatment, and at 6 month follow-up, a mean decrease of 30.2% in YBOCS scores was observed (68). Similarly there are some preliminary data suggesting that CBT can be used in children who have not responded to previous medication and adequate CBT trial (54, 56, 69). This area requires further exploration in detail since current available options for treatment in childhood OCD are limited.

Predictors of Response to CBT

Data from adult OCD reports that base line symptom severity, symptom

subtype (like sexual/religious obsessions and hoarding), severe depression, the presence of comorbid personality disorders, family dysfunction, and poor therapeutic alliance have been associated with poor outcome of CBT (72, 73). Similarly comorbid illness adversely impacted response to pharmacotherapy in pediatric OCD and significantly increased risk of relapse following withdrawal from pharmacotherapy treatment (74).

Conceptually speaking, comorbid conditions in pediatric OCD like depression, anxiety disorders, ADHD, ODD and tic disorder may hamper the progress of CBT (3). For example, ADHD symptoms may interfere during the CBT sessions, while a child suffering from ODD may resist engaging in CBT treatment. Similarly, a developmental delay, mental retardation, and very young children may not be able to participate effectively in CBT (34). Prognostic indicators of positive response to CBT comprise willingness to cooperate with treatment, presence of overt rituals, motivation to put efforts into therapy to eliminate rituals and ability to recognize, monitor and report symptoms (42). A review by Piacentini et al (63), revealed that baseline severity of obsessions and OCD-related difficulties in academics were associated with poor treatment outcome, while age, gender, baseline medication status, comorbid symptomatology or therapist experience did not have any impact on the CBT treatment outcome. Another study by Barrett et al (53), revealed that higher pretreatment severity and higher family dysfunction predicted worse long-term outcome on CBT.

In a study by March et al, presence of comorbid tic disorder, predicted a poorer outcome in the medication alone (sertraline) group, but not in CBT groups (75). Similarly, another study by Himle et al, found that presence of

comorbid tic disorder did not impact BT response (76). It appears that a comorbid tic disorder does not have any impact on CBT and BT outcome. Similarly, Storch et al, found that anxiety as a comorbidity did not impact CBT response in 38 adolescents (77). Children are known to have poor insight into their symptoms, but there is no data on the effect of insight on CBT outcome. Overall, only a small number of studies report the predictors of therapeutic change, hence limiting our understanding of the effectiveness of CBT in children and adolescents with OCD. Further research delineating the role of psychopathology, comorbidity, insight and temperamental characteristics may be helpful in determining the predictors of CBT outcome.

Long-term Efficacy of CBT

A study by Barrett et al, reported that treatment gains were maintained, with a total of 70% of participants in individual therapy and 84% in group therapy were diagnosis free at 18-month follow-up (53). Similar studies by Franklin et al, and March et al, reported that improvements of more than 50% on CY-BOCS at mean 9-month follow-up (36) and mean 18-month follow-up (43) respectively. In a study of manual-guided CBT, mean reduction of symptoms up to 69% was maintained at 6-month follow-up (58). There is a paucity of literature with regard to efficacy of long term outcome of CBT. Available preliminary data suggests that CBT appears to have role in relapse prevention and maintenance treatment (57,78, 79).

Conclusions

The review of the extant literature clearly shows that CBT is a promising treatment option for pediatric OCD and that a combination of CBT and medication or CBT alone can be considered as the first line of treatment. The

choice of treatment - CBT alone, a combination of CBT and medicines or medicines alone - is also influenced by several variables such as patient (family members') preference, availability of resources (particularly for CBT), costs involved, time constraints, past history of treatment response and side effects of treatments, cognitive capacity to understand CBT procedures, comorbid psychiatric disorders, symptom severity, family support, and family pathology. In India, there is a severe scarcity of mental health professionals who can offer CBT. Very few academic institutes can offer CBT to a selected group of patients. In view of this, medications are often the first line of treatment for pediatric OCD in developing countries like India.

There is however a need to replicate the findings of the POTS study to establish the efficacy of CBT and its combination with medication over medication alone. Future studies should also consider examining any variation in results of CBT administration among pediatric and adolescent population. Data on the role of CBT in partial responders and nonresponders to medications is limited and there is therefore an urgent need to examine the role of CBT in such populations given the extensive clinical implications. The study of long-term efficacy of CBT in treating pediatric OCD is a priority area of research. Lastly, research is needed to evaluate mediators and moderators of treatment response.

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Obsessive Compulsive Disorder

Current Understanding and Future Directions

Until about two decades ago, obsessive-compulsive disorder (OCD) was considered an uncommon mental illness for which no effective treatment existed. Since then, there has been significant progress in the understanding and treatment of OCD. Recent developments in the field of neuroimaging, genetics and immunology have resulted in newer insights into this disorder. Learning and cognitive theories have contributed to specific treatment approaches. This book brings together some of the recent developments in the field and offers ideas to future research. The contributors to this book are well-known researchers in the area.

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