Seminar

Obsessive-compulsive disorder

Dan J Stein

Obsessive-compulsive disorder is a frequent, chronic, costly, and disabling disorder that presents in several medical settings, but is under-recognised and undertreated. For many years, obsessive-compulsive neurosis was seen as a disorder that provided an important window on the workings of the unconscious mind. Today, obsessive-compulsive disorder is viewed as a good example of a neuropsychiatric disorder, mediated by pathology in specific neuronal circuits, and responsive to specific pharmacotherapeutic and psychotherapeutic interventions. In the future we can expect more precise delineation of the origins of this disorder, with integration of data from neuroanatomical, neurochemical, neuroethological, neurogenetic, and neuroimmunological research.

Obsessive-compulsive disorder was once considered a rare condition, but is now viewed as not only one of the more prevalent psychiatric disorders,[1] but also one of the most disabling medical disorders.[2] Previously, obsessive-compulsive neurosis was described in terms of unconscious conflict. Today, it is regarded as a neuropsychiatric disorder mediated by specific neuronal circuitry and closely related to neurological conditions such as Tourette's syndrome and Sydenham's chorea.[3]

Description

Symptoms

Obsessive-compulsive disorder is characterised by intrusive thoughts or images (obsessions), which increase anxiety, and by repetitive or ritualistic actions (compulsions), which decrease anxiety. The most recent revision of the diagnostic criteria for obsessive-compulsive disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[4] emphasises that compulsions can be observable behaviours or mental rituals (panel 1).

The most frequent symptoms in obsessive-compulsive disorder are contamination concerns with consequent washing, or concerns about harm to self or others with consequent checking. Factor analysis[5] has shown additional subgroups such as a cluster of symptoms of symmetry concerns and arranging rituals, and a cluster focused on hoarding (panel 2). However, many obsessions and compulsions have been identified, including sexual, religious, somatic, and musical symptoms.[6]

The symptoms of obsessive-compulsive disorder symptoms have varied little by time (pathological scrupulosity, for example, has long been documented) or place (similar symptoms are seen across many cultures).[7] Although the predominant symptoms can change with time in any individual,[8] symptoms do not differ by much between children and adults (although they may reflect developmental level, for example, children may have more concrete types of ritual).

Symptoms do, however, differ in patients with and without tics,[9] perhaps pointing to psychobiological differences. Although patients generally recognise the excessiveness of their symptoms, their insight is varied and some are judged as having poor insight. Lack of insight in obsessive-compulsive disorder symptoms might be associated with frontal lesions.[10,11] Patients with obsessional slowness could have another type of obsessive-compulsive disorder characterised by a greater degree of neurological impairment.[12]

Diagnosis

The DSM-IV criteria for obsessive-compulsive disorder state that symptoms should not be due to a general medical disorder or a substance. Obsessive-compulsive symptoms have been associated with various neurological lesions of the cortico-striatal-thalamic-cortical circuits, which can arise after administration of dopamine agonists (such as methylphenidate or cocaine), or after streptococcal infection (presumably on an autoimmune basis).

To be clinically significant, symptoms of obsessive-compulsive disorder must be accompanied by marked distress and dysfunction.[13] Subclinical obsessive-compulsive symptoms are not uncommon, and are seen during the course of normal development. Patients with obsessive-compulsive disorder, however, can cause substantial impairment, including severely affected quality of life.[14]

Obsessions and compulsions should not be confused with the inflexible character traits that comprise obsessive-compulsive personality disorder. Although the distinction between axis I (eg, a syndrome such as obsessive-compulsive disorder) and II (eg, a personality disorder such as obsessive-compulsive personality disorder) disorders is unclear at times, the obsessions and compulsions of obsessive-compulsive disorder differ qualitatively from obsessive-compulsive personality traits such as perfectionism and overconscientiousness.

Selection criteria and search strategy

I searched Medline up to 2001 for relevant articles using the terms obsession, compulsion, and obsessive-compulsive to aim at objective coverage; but references for this article were chosen more subjectively to illustrate data and themes in description, pathogenesis, pharmacotherapy, and psychotherapy of obsessive-compulsive disorder

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Department of Psychiatry, University of Stellenbosch, Cape Town, and University of Florida, Gainesville (Prof Dan J Stein MBChB)
(e-mail: djs2@sun.ac.za)

Similarly, despite the occasional overlap, the symptoms of obsessive-compulsive disorder differ clearly from the fears and worries seen in other anxiety disorders, from the ruminations characteristic of mood disorders, and from the delusions of psychotic disorders.

Panel 1: **DSM-IV diagnostic criteria for obsessive-compulsive disorder***

A Either obsessions or compulsions

Obsessions as defined by:

- Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
- The thoughts, impulses, or images that are not simply excessive worries about real-life issues
- The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralise them with some other thought or action
- The person recognises that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions as defined by:

- Repetitive behaviours (eg, hand-washing, ordering, checking) or mental acts (eg, praying, counting, repeating words silently) that the person feels driven to do in response to an obsession, or according to rules that must be applied rigidly
- The behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralise or prevent or are clearly excessive

B At some point during the course of the disorder, the person has:

Recognised that the obsessions or compulsions are excessive or unreasonable. (Note: this definition does not apply to children)

C The obsessions or compulsions:

Cause marked distress
Are time consuming (take longer than 1 h a day),
Or greatly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships

D If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it—eg,

Preoccupation with food in the presence of an eating disorder;
Hair pulling in the presence of trichotillomania;
Concern with appearance in the presence of body dysmorphic disorder;
Preoccupation with drugs in the presence of a substance use disorder;
Preoccupation with having a serious illness in the presence of hypochondriasis;
Preoccupation with sexual urges or fantasies in the presence of a paraphilia;
Or guilty ruminations in the presence of major depressive disorder)

E The disturbance is not due to the direct physiological effects of a substance (eg, a drug of abuse, a medication) or a general medical condition

Specify if:
with poor insight: if, for most of the time during the current episode, the person does not recognise that the obsessions and compulsions are excessive or unreasonable

*Adapted from reference 4.

Obsessive-compulsive or stereotypic symptoms are an intrinsic component of many disorders, including autism, Tourette's syndrome, and frontal lobe lesions. Conversely, some disorders have a restricted focus on symptoms that can be seen in obsessive-compulsive disorder. For example, patients with body dysmorphic disorder (concerns about imagined ugliness) and hypochondriasis (concerns about imagined illness) have somatic obsessions and compulsions. Disorders with overlapping characteristics and psychobiology to obsessive-compulsive disorder fall within a putative spectrum of obsessive-compulsive disorders.[15]

Epidemiology

The Epidemiological Catchment Area study[16] provided the first epidemiological data for obsessive-compulsive disorder that were based on a nationally representative sample and reliable diagnostic criteria. Obsessive-compulsive disorder was the fourth most prevalent psychiatric disorder, with a lifetime prevalence of 2·5%.[16] Results of a cross-national study[1] with similar methods showed that prevalence did not differ by much across many different populations. A review[17] of community studies suggested that despite some concerns about the validity of the diagnosis of obsessive-compulsive disorder in the Epidemiological Catchment Area study, obsessive-compulsive disorder is not uncommon in adults[18] and children,[19] with many findings showing a prevalence similar to that recorded in the Epidemiological Catchment Area study.

The male to female ratio of obsessive-compulsive disorder is roughly the same, by contrast with many other anxiety and mood disorders, in which prevalence is higher in females than males. Age of onset in obsessive-compulsive disorder has a bimodal distribution. In some patients, this disorder starts at puberty or earlier; juvenile onset obsessive-compulsive disorder is especially common in males, and has other distinguishing characteristics such as greater familiality and relation to tic disorders.[20] Other patients can have later onset, for example, after pregnancy, miscarriage, or parturition.[21,22]

Results of epidemiological studies[23] are consistent with those of clinical work showing that obsessive-compulsive disorder has a high comorbidity with other anxiety and mood disorders. These findings also suggest that some patients with obsessive-compulsive disorder have impulsive features, including symptoms of childhood conduct disorder and an increased rate of suicide attempts.[23]

Although acute episodes of obsessive-compulsive disorder have been documented, the illness is generally chronic.[24] Furthermore, obsessive-compulsive disorder is associated with substantial direct and indirect costs,[25] which are compounded by an absence of recognition, and by underdiagnosis and inappropriate treatment. Patients might be too embarrassed to visit a clinician, or might not be aware that help is available; in one survey,[26] the lag time from symptom onset to correct diagnosis was 17 years.

Panel 2: **Subgroups of obsessions and compulsions in obsessive-compulsive disorder**

Obsessions	Compulsions
Contamination concerns	Washing, bathing, showering
Harm to self/others, sexual/religious concerns	Checking, praying, asking for reassurance
Symmetry, precision concerns	Arranging, ordering
Saving concerns	Hoarding

Assessment

Since patients frequently conceal their symptoms,[27] it is important to be aware of the possible presentation of obsessive-compulsive disorder in many medical settings, and to screen patients routinely using questions for obsessions ("Do you have unpleasant thoughts that keep coming into your mind, even though you don't want them?") and compulsions ("Do you have to do things over and over, even though you don't want to?"). In dermatology clinics, for example, washing rituals are frequent. Patients presenting for cosmetic surgery sometimes have somatic concerns, patients in general medical clinics can have symptoms of hypochondriasis, neurology patients with involuntary movement disorders (Tourette's syndrome, Sydenham's chorea, Huntington's disorder) or cortico-striatal-thalamic-cortical lesions may have comorbid obsessive-compulsive disorder, children can have obsessive-compulsive disorder after streptococcal infection, and pregnant women can have de novo or increased obsessive-compulsive disorder symptoms.

To assess obsessive-compulsive disorder, a thorough psychiatric history and examination should be taken to investigate symptoms of this and comorbid disorders, and to allow a differential diagnosis from other anxiety, mood, and psychotic disorders. A general medical history and examination should also be obtained; comorbid tics are not uncommon and should be assessed, and in some patients, symptoms of obsessive-compulsive disorder begin after infection.[28] Indications for special investigations such as structural brain imaging might include late onset, atypical symptoms, or severe treatment refractoriness.

The severity of symptoms can be measured with several rating scales including the Yale-Brown obsessive-compulsive scale,[29] which is sufficiently user-friendly to be easily administered in clinical practice, and the reliability and validity of this scale have made it the gold standard in randomised controlled trials of obsessive-compulsive disorder. The scale has also been adapted for use in children and adolescents.

It may be useful to inquire about the patient's own explanation for their disorder—what are their theories about its cause and treatment? Patients with scrupulosity, for example, could see their symptoms in religious terms.[30] Some patients have a view that unconscious conflict is a cause of symptoms. Being aware of such models, and offering an alternative perspective, is a key step in starting treatment. Consumer advocacy groups[31] and internet groups[32] can usefully contribute to such psychoeducation.

Pathogenesis

Neuroanatomy

The earliest indication that obsessive-compulsive disorder is mediated by specific neuronal circuits probably came from work showing an association between post-encephalitis parkinsonian and obsessive-compulsive symptoms together with striatal lesions.[33] Symptoms of obsessive-compulsive disorder have also been documented in various neurological disorders with striatal involvement, including Tourette's syndrome, Sydenham's chorea, Huntington's disorder, and Parkinson's disorder.[34]

Conversely, patients with obsessive-compulsive disorder can have abnormalities in a broad series of measures and paradigms used in neuropsychiatric (eg, neurological soft signs, olfactory identification, evoked potentials, prepulse inhibition, intracortical inhibition) and neuropsychological (eg, executive function, visual memory function) studies,[34,35] These abnormalities are consistent with cortico-striatal-thalamic-cortical dysfunction and impaired inhibition, and some evidence suggests that they are specific to obsessive-compulsive disorder.[36]

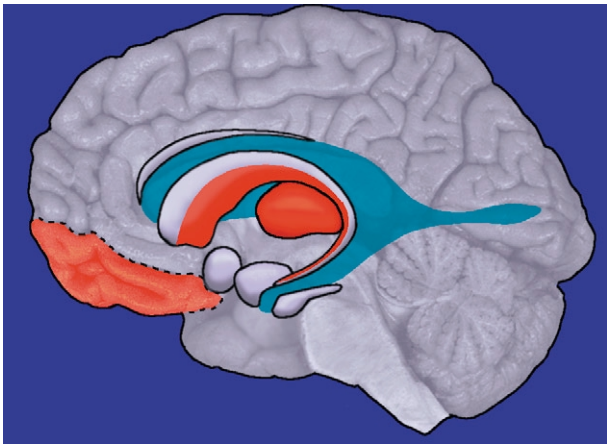

Figure 1: **Increased activity in orbitofrontal cortex and caudate in patients with obsessive-compulsive disorder**
Reproduced with permission of the University of Stellenbosch.

Advances in brain imaging have, however, provided the most persuasive neuroanatomical data for obsessive-compulsive disorder.[37] In some studies, structural imaging has shown abnormalities such as decreased volume or increased grey matter density in cortico-striatal-thalamic-cortical circuits. Functional imaging has consistently shown that obsessive-compulsive disorder is characterised by increased activity in orbitofrontal cortex, cingulate, and striatum at rest, and especially during exposure to feared stimuli (figure 1). The application of molecular imaging methods to obsessive-compulsive disorder is at an early stage,[38] but lends support to structural and functional findings.

Other regions of the brain might also play a part in obsessive-compulsive disorder. For example, temporal dysfunction has been associated with obsessive-compulsive disorder,[39,40] and there is some evidence of amygdala involvement in obsessive-compulsive disorder.[41] Imaging research in children has supported the involvement of cortico-striatal-thalamic-cortical circuits in obsessive-compulsive disorder, and could ascertain the evolution of brain abnormalities in different regions over time.[42]

Pharmacotherapy and behavioural therapy can both normalise activity in cortico-striatal-thalamic-cortical circuits[43] (figure 2). These data have crucial implications for an integrated view of the mind and body. Baseline activity differentially predicts response to pharmacotherapy and to psychotherapy,[44] so that different methods may be effective via different mechanisms. Neurosurgical interruption of cortico-striatal-thalamic-cortical circuits can also reduce symptoms[45] and decrease striatal volume.[46]

Neurochemistry

The serotonin system is probably involved in mediation of obsessive-compulsive disorder. The earliest evidence for such a mechanism was the finding that clomipramine, a tricyclic antidepressant that is mainly a serotonin reuptake inhibitor, was effective in treatment of obsessive-compulsive disorder.[47] Administration of clomipramine was accompanied by a decrease in concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with obsessive-compulsive disorder.[48]

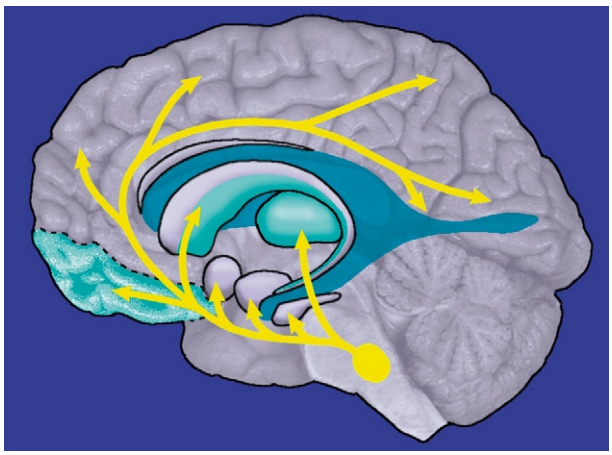

Figure 2: **Normalisation of cortico-striatal-thalamic-cortical circuits by either pharmacotherapy or psychotherapy in obsessive-compulsive disorder**
Yellow lines are the serotonergic neurons originating in the raphe, and projecting widely to cortico-striatal-thalamic-cortical circuits and other regions. Reproduced with permission of the University of Stellenbosch.

Results of studies[49] of static measures of serotonergic function in obsessive-compulsive disorder have, however, been inconsistent, and other work has focused on more informative dynamic measures. Thus, for example, administration of the serotonin (5-HT) agonist m-chlorophenylpiperazine (mCPP) has been accompanied by exacerbation of obsessive-compulsive disorder symptoms and a blunted neuroendocrine response. After treatment with a serotonin reuptake inhibitor, behavioural and neuroendocrine responses to mCPP seem to be normal.

This work leads to questions about the role of specific 5-HT subreceptors in obsessive-compulsive disorder. Effects of mCPP on the postsynaptic 5-HT_{2C} receptor, for example, may be especially relevant.[50,51] Preclinical and clinical data also suggest that the 5-HT_{1D} terminal autoreceptor plays an important part; desensitisation of this receptor in the orbitofrontal cortex needs high duration and high dose administration of serotonin reuptake inhibitors.[52] Preliminary challenge,[53] pharmacological,[54] genetic,[55] and imaging[56] data lend support to a role for 5-HT_{1D} in obsessive-compulsive disorder.

Although work on the role of the serotonin system in mediation of obsessive-compulsive disorder is important, to date no specific abnormality in the serotonin system has been identified as a cause. Indeed, many other systems, including glutamate neurotransmission,[57] some neuropeptides,[58] and gonadal steroids[22,59] also play a part. Ultimately, the role of second and third messenger pathways in obsessive-compulsive disorder will need to be delineated.[60–62]

One cortico-striatal-thalamic-cortical neurotransmitter system that could be especially important in mediation of obsessive-compulsive disorder in some patients is dopamine.[63] In preclinical studies, administration of dopamine agonists leads to stereotypic behaviour, whereas in human beings, such agents can exacerbate symptoms and tics of obsessive-compulsive disorder. Conversely, dopamine blockers are used in treatment of Tourette's syndrome, one of the spectrum of obsessive-compulsive disorders. Furthermore, augmentation of serotonin reuptake inhibitors with such agents can be useful in treatment-refractory obsessive-compulsive disorder.

Neurogenetics[4]

Early work suggesting that obsessive-compulsive disorder has a familial component has been confirmed by more recent rigorous studies[64] in which investigators used structured diagnostic interviews of probands and controls. Also, results of some studies[65] have shown a genetic relation between obsessive-compulsive disorder and Tourette's. Patients with symptoms of obsessive-compulsive disorder but a family history of Tourette's can have neurobiological dysfunction more similar to Tourette's than to primary obsessive-compulsive disorder.[66]

Attention has begun to focus on the possibility that functional genetic polymorphisms have a role in the pathogenesis of obsessive-compulsive disorder.[67] Early work suggested a sexually dimorphic association with low activity in catechol-O-methyltransferase (COMT) alleles, but subsequent reports have been inconsistent.[68] Another sexually dimorphic association, with an allele of the monoamine oxidase-A (*MAO-A*) gene, also deserve further investigation.

Work on polymorphisms of serotonin system genes such as the serotonin transporter has also been published, but to date has not proved consistent.[69] Early data for the 5-HT_{1D} polymorphism[55] is especially interesting in view of other evidence that the terminal autoreceptor has an important role in mediation of obsessive-compulsive disorder, but remains to be replicated.

Recent work has also focused on dopaminergic polymorphisms, indicating that alleles were distributed differently in patients with obsessive-compulsive disorder with and without tics.[70] Such work could ultimately provide the basis for a rational approach to delineation of the heterogeneity of obsessive-compulsive disorder, including differences in characteristics of the disease and treatment response.

Neuroimmunology

Early reports of an association between obsessive-compulsive disorder and Sydenham's chorea were confirmed in a systematic investigation,[71] leading to consideration of whether some cases of obsessive-compulsive disorder resulted from autoimmune processes that disrupted cortico-striatal-thalamic-cortical circuits. Indeed, the term autoimmune neuropsychiatric disorder associated with streptococcal infections, or PANDAS, has been coined to describe children who have acute onset of obsessive-compulsive disorder symptoms with or without tics after streptococcal infection.[28]

This contribution was followed by a series of studies[72] exploring various aspects of an autoimmune hypothesis of obsessive-compulsive disorder. Patients with PANDAS, for example, have abnormal striatal volume on brain imaging. Furthermore, their obsessive-compulsive disorder and tic symptoms respond to immunomodulatory interventions such as plasma exchange and intravenous immunoglobulin. Long-term follow-up showed continued improvement of symptoms for most patients, especially when antibiotic prophylaxis had been effective in prevention of recurrent streptococcal infections.

A next step in work on the autoimmune hypothesis of obsessive-compulsive disorder is to establish the precise immunological mechanisms. In some studies,[73] expression of D8/17, a B lymphocyte antigen and marker of susceptibility to development of sequelae after streptococcal infection, was increased in patients with obsessive-compulsive disorder. Furthermore, some

investigators[74] have shown evidence of several immune dysfunctions in obsessive-compulsive disorder, including abnormal autoantibodies.

The putative association between immune dysfunctions and obsessive-compulsive disorder needs further study to determine its specificity (versus other disorders),[75] its frequency (compared with other possible striatal insults), and its relation to other psychobiological factors (such as genetic variables).[76] Nevertheless, such work has already strengthened the present view of obsessive-compulsive disorder as a neuropsychiatric disorder, and could ultimately lead to identification of at-risk children and of new treatments.

Neuroethology

Development of animal models that can be used to help search for new pharmacotherapeutic agents for obsessive-compulsive disorder remains an important goal for the future. In the interim, however, many investigators have suggested that symptoms of obsessive-compulsive disorder are redolent of animal stereotypies (repetitive non-functional motor behaviour), that the striatum is a repository for patterned motor sequences, and that the neurochemistry mediating stereotypies overlaps with that of obsessive-compulsive disorder.[77]

An intriguing set of animal models is that found in veterinary behavioural practice.[78] Acral lick dermatitis in dogs, for example, is characterised by repetitive licking of the paws that is reminiscent of some cases of obsessive-compulsive disorder in which the hands are licked rather than washed. The disorder is more common in some canine families than others, and its pharmacotherapy response profile is very similar to that of obsessive-compulsive disorder.[79]

Other findings[77] suggest a role for environmental factors in promotion of stereotypies. Stereotypic behaviour can, for example, be induced by confinement or by emotional deprivation. Interestingly, primates raised under conditions of deprivation have abnormalities in striatal architecture.[80] The selective serotonin reuptake inhibitor fluoxetine is more effective than placebo in the pharmacotherapy of stereotypies in primates who are emotionally deprived.[81]

Indeed, an ethological perspective (one that is affected by studies of animal behaviour) has generated several hypotheses about obsessive-compulsive disorder. Although speculative, these hypotheses are valuable in that they help to supplement work on the proximate mechanisms of obsessive-compulsive disorder, with ideas about its evolutionary underpinnings. One thought-provoking set of research has focused on disgust;[82] fear and disgust are mediated by different pathways—although the amygdala is crucial in mediation of fear in many anxiety disorders, cortico-striatal-thalamic-cortical and other circuits could be responsible for impairments in disgust processing in obsessive-compulsive disorder.

Integration

Much evidence emphasises the role of cortico-striatal-thalamic-cortical circuits in mediation of obsessive-compulsive disorder. Further work is, however, needed to establish the exact origins and nature of such dysfunction; such research needs to incorporate a broad range of data, including neuroanatomical, neurochemical, neurogenetic, neuroimmunological, and neuroethological variables. Until then, attempts can be made to integrate what is known about the role of cortico-striatal-thalamic-cortical circuits in general with an understanding of obsessive-compulsive disorder.

An early neuroanatomical hypothesis, for example, was that caudate abnormalities were associated with cognitive symptoms (such as are apparent in obsessive-compulsive disorder), whereas putamen dysfunction led to sensorimotor symptoms (such as the tics of Tourette's).[37] However, results of imaging studies[42] suggest that many cortico-striatal-thalamic-cortical circuits are involved in obsessive-compulsive disorder. Possibly, specific projection fields or cell types are involved in specific kinds of symptoms.

Certainly, cortico-striatal-thalamic-cortical circuits have a role in mediation of development, maintenance, and selection of procedural strategies.[83,84] Ventral cortico-striatal-thalamic-cortical circuits have a central role in recognition of stimuli that are behaviourally significant (and in error detection) and in regulation of autonomic and goal-directed responses (including response inhibition and suppression of negative emotion),[37,85,86] and might therefore be especially important in obsessive-compulsive disorder.

Perhaps obsessive-compulsive disorder results from an inability to inhibit procedural strategies mediated by cortico-striatal-thalamic-cortical circuits from intruding into consciousness. Such a view is consistent with three observations. First, the limited number of symptom themes in obsessive-compulsive disorder and their apparent evolutionary importance. Second, dysfunction of cortico-striatal-thalamic-cortical circuits in obsessive-compulsive disorder, with activation of temporal rather than striatal regions during implicit cognition.[87] And third, the role of the serotonin system in cortico-striatal-thalamic-cortical circuits, since the serotonin system is thought to play an important part in mediation of inhibitory processes.

Pharmacotherapy

Introduction of selective serotonin reuptake inhibitors provided the potential for agents that are not only effective for obsessive-compulsive disorder, but that also have a better safety and tolerability profile than does clomipramine. Indeed, all available serotonin selective reuptake inhibitors are effective and well tolerated in randomised controlled studies of obsessive-compulsive disorder,[88] and several are also effective in obsessive-compulsive disorder in children.[89] By contrast, despite occasional positive trials, agents from other drug classes (monoamine oxidase inhibitors, benzodiazepines, dopamine blockers) have not consistently been effective in monotherapy of obsessive-compulsive disorder.

Results of meta-analyses[90,91] of obsessive-compulsive disorder trials suggest that less selective agents such as clomipramine have a greater effect size than do more selective agents. However, the methods of these meta-analyses had many limitations, and, to date results of all head-to-head studies have suggested equivalence in efficacy and tolerability of serotonin reuptake inhibitors in obsessive-compulsive disorder.[88] Some agents with substantial serotonin reuptake inhibition (eg, venlafaxine), might also be effective in obsessive-compulsive disorder, but have not yet been rigorously studied. Inositol, an agent that acts directly at a second messenger level, has been used mainly in research settings.

Few investigators have done fixed-dose studies of serotonin reuptake inhibitors in obsessive-compulsive disorder, and these have not always yielded similar conclusions. Nevertheless, a general impression, supported by clinical consensus,[92,93] is that a serotonin reuptake inhibitor trial of long duration (10–12 weeks) and high dose (increasing gradually, at 2–4 weekly

Panel 3: **Recommended dose ranges of serotonin selective reuptake inhibitors for obsessive-compulsive disorders**

Drug	Dose range
Citalopram	20–60 mg/day
Fluoxetine	20–60 mg/day
Fluvoxamine	50–300 mg/day
Paroxetine	20–50 mg/day
Sertraline	50–200 mg/day

intervals, to maximum recommended dose) should be prescribed (panel 3). Early side-effects might even be positive predictors of response.[94] However, several negative predictors have been described, including hoarding symptoms, comorbid tics, and schizotypal personality disorder—consistent with evidence that the dopamine system is important in their mediation.

Although response to treatment does not necessarily imply remission of symptoms,[95] it could be associated with a large improvement in quality of life. After poor response to an adequate trial, options include changing to a different serotonin reuptake inhibitor (a usual first step) or augmentation (most relevant when there is part response). The best evidence for augmentation of serotonin reuptake inhibitors is for low doses of dopamine blockers; earlier work was undertaken with traditional neuroleptics[96] and more recent work has confirmed the value of better tolerated new generation antipsychotic agents[97] in adults.

Combinations of antidepressants have been useful in some studies of adults (controlled) and children (uncontrolled). Various augmenting agents from other classes (eg, lithium, buspirone, pindolol, inositol) have also been assessed in controlled trials of adult obsessive-compulsive disorder, but to date, findings have been negative or inconsistent. In patients resistant to treatment, several monotherapy and augmentation approaches can be considered, but to date perhaps most data support use of intravenous clomipramine in adults.[98]

Pharmacotherapy in obsessive-compulsive disorder should be maintained for at least a year.[92] The possibility that some patients maintain responses at a lower dose must be weighed against the possibility that reinstatement of treatment after relapse can be associated with a poorer response.[99] Once the decision is made to discontinue the drugs, it would seem reasonable to do this gradually (eg, decreasing dose by 25% every few months).

Psychotherapy

Psychoanalytical treatment for obsessive-compulsive neurosis was suggested by Freud,[3] and for a long time was thought to be an effective approach to management. However, despite the contribution of investigators in delineation of the characteristics and psychology of obsessive-compulsive disorder, at present, insufficient data support use of psychoanalytical treatment.

Behavioural therapy was the first psychotherapy for which careful empirical support was obtained,[100] and is useful in obsessive-compulsive disorder in adults and children. An important component of behavioural therapy is exposure to the feared stimuli. The precise way in which exposure results in normalisation of cortico-striatal-thalamic-cortical circuitry remains, however, to be fully understood.

Cognitive interventions might also have a role in treatment of obsessive-compulsive disorder.[101] Consensus ratings suggested that several belief domains are important in obsessive-compulsive disorder, including inflated responsibility; overimportance of thoughts; excessive concern about the importance of controlling thoughts; and overestimation of threat.[102] Cognitive approaches are as effective as exposure procedures.[103]

In practice, a cognitive-behavioural approach is often used, administered individually or in groups,[104] with the contexts ranging from self-help computer instruction through to treatment in an intensive care unit.[105] Because symptoms of obsessive-compulsive disorder can greatly affect the patient's family, assessment of such an effect and inclusion of the patient's partner or family in development of a treatment strategy would seem appropriate in some cases.[106]

Unfortunately, few investigators have assessed how best to sequence or combine pharmacotherapy and psychotherapy for obsessive-compulsive disorder. Nevertheless, from a theoretical viewpoint, integration of different approaches could be useful.[107] In clinical practice, it would seem sensible to encourage patients who are on drugs to also understand and adhere to the principles of cognitive-behavioural therapy, and the results of several studies lend support to this idea.[108,109]

The spectrum of obsessive-compulsive disorders

Disorders that overlap with obsessive-compulsive disorder are postulated to lie on an obsessive-compulsive disorder spectrum of conditions. Several different approaches to such a spectrum have been formulated.[110] Freud postulated that there was a spectrum from obsessive-compulsive personality to obsessive-compulsive neurosis to psychosis. Although this idea is no longer popular, there is still an interest in patients with obsessive-compulsive disorder and poor insight, and in psychotic patients with comorbid obsessive-compulsive disorder.[111,112]

More recently, attempts to characterise the obsessive-compulsive disorder spectrum have emphasised neurobiological findings, including neurogenetic approaches[113] in which obsessive-compulsive disorder might be related to Tourette's, pharmacotherapeutic dissection approaches that emphasise the range of disorders that respond selectively to serotonin reuptake inhibitors,[114] and neuroanatomical approaches that postulate a spectrum of striatal disorders.[115]

Another approach has been to highlight the distinction between compulsive and impulsive disorders. Compulsive disorders such as body dysmorphic disorder are characterised by exaggerated harm concerns, impulsive disorders involve underestimation of risk, and some disorders such as Tourette's have both compulsive and impulsive features. Such a contrast is clearly overly simplistic, but could have some heuristic value (for example, compulsive disorders have features of increased frontal and serotonergic activity, whereas impulsive disorders have features of decreased frontal and serotonergic function).[116]

Part of the value of delineating a putative spectrum of obsessive-compulsive disorders, is that assessment and treatment of some disorders closely follows that of obsessive-compulsive disorder. Body dysmorphic disorder, for example, has many features in common with obsessive-compulsive disorder, and responds to both serotonin reuptake inhibitors and cognitive-behaviour treatment.[117] Furthermore, obsessive-compulsive or stereotypic symptoms in various disorders can also respond to serotonin reuptake inhibitors.[118] However, disorders that lie at the more impulsive end of the

obsessive-compulsive disorder spectrum may need different forms of pharmacotherapy and psychotherapy than those used for obsessive-compulsive disorder.

Recommendation

Although many advances have already been made in treatment of obsessive-compulsive disorder, in the future a better understanding of the pathogenesis of obsessive-compulsive disorder will hopefully lead to further expansion of the present range of treatments, including innovations in psychopharmacology, psychotherapy, and other modalities of intervention.[119,120]

Conflict of interest statement

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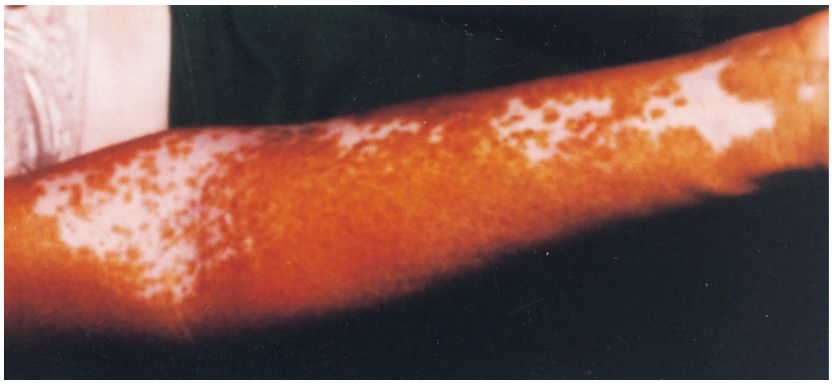
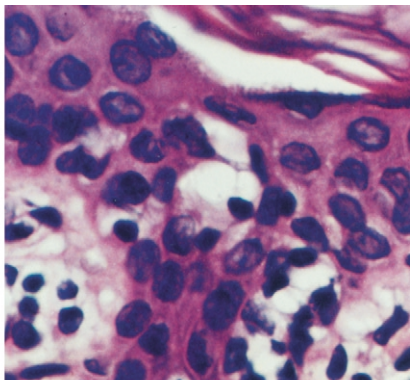
Clinical picture

Vitiligo

Leopold Montes, Roswell Pfister, Walter Wilborn, Francisco Elizalde





A 35-year-old woman presented with generalised spreading vitiligo affecting her face, trunk, and extremities (figure, left). The depigmented macules were slightly pruritic and fluorescent under Wood's light examination. Skin biopsies showed lack of melanin in the basal cell layer and vacuolisation of epidermal cells (figure, right, haematoxylin and eosin ×650). A dermal inflammatory infiltrate composed mainly of lymphocytes was present near the epidermo-dermal junction. Numerous Langerhans cells were present in both epidermis and dermis. The basement membrane was discontinuous and irregular, another typical feature of vitiligo.

Vitiligo Unit, Paraguay 2302, 1121 Buenos Aires, Argentina (L Montes MD, R Pfister MD, W Wilborn MD, F Elizalde MD)