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Clinical review

Obsessive-compulsive disorder

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Obsessive-compulsive disorder is one of the more common serious mental illnesses. The shame and secrecy associated with it, as well as lack of recognition of its characteristic symptoms, can lead to delay in diagnosis and treatment. Effective psychological and drug treatments are available for the distressing, time consuming, repetitive thoughts and rituals and the associated functional impairment. This article reviews the presentation and assessment of obsessive-compulsive disorder and discusses the current best treatment options, as well as directions for the future.

Methods

We searched for the term "obsessive compulsive disorder" in electronic databases and referred to published systematic reviews, including the recently published guideline from the National Institute for Health and Clinical Excellence (NICE).

Who gets it and why does it matter?

Obsessive-compulsive disorder occurs throughout the life span, and children as young as 6 or 7 present with the characteristic impairing symptoms (box 1). At the other end of the age range, patients may present for the first time in old age. Most adults with the disorder report onset in childhood or adolescence. The condition can result in considerable disability; for example, children may drop out of education and adults can become housebound. The World Health Organization rates obsessive-compulsive disorder as one of the top 20 most disabling diseases. If untreated, it generally persists,¹ yet effective, evidence based psychological and drug treatments are available.

Recent epidemiological studies report prevalence rates of 0.8% in adults and 0.25% in 5-15 year old children,²⁻³ although earlier studies suggested rates as high as 1-3% in adults and 1-2% in children and adolescents.

Why do clinicians need to know about it?

People of all ages with obsessive-compulsive disorder understand the senseless nature of their repetitive, unwanted behaviours and intrusive, recurrent thoughts. This may lead to shame, reluctance to seek help, and poor recognition by health professionals. People with the disorder have long delays in accessing effective treatments—17 years on average in one study.⁴ They frequently present to non-psychiatrists for treatment (table 1), and psychiatric symptoms go undetected. Greater awareness of the condition is

Summary points

Obsessive-compulsive disorder can occur at any age but most often presents for the first time in adolescence

Long delays in diagnosis often occur, and the shame associated with the disorder may inhibit people from mentioning the symptoms

General practitioners should ask specific screening questions if obsessive-compulsive disorder is suspected

Mild cases may be helped by guided self help; most people with obsessive-compulsive disorder should be offered cognitive behaviour therapy incorporating exposure and response prevention

Children and adults with obsessive-compulsive disorder may be offered selective serotonin reuptake inhibitor drugs; this should be a second line treatment in young people

The condition may remit, but can be relapsing or chronic; people with obsessive-compulsive disorder who relapse should have rapid access to services

needed in a range of non-psychiatric healthcare settings, and clinicians need to be confident about recognising it.

What are the symptoms?

Obsessions are unwanted ideas, images, or impulses that repeatedly enter a person's mind. Although recognised as being self generated, they are experienced as "egodystonic" (out of character, unwanted, and

Table 1 Non-psychiatrists likely to see patients with obsessive-compulsive disorder (OCD)

Professional	Reason for consultation
General practitioner	Depression, anxiety
Dermatologist	Chapped hands, eczema, trichotillomania
Cosmetic surgeon	Concerns about appearance (body dysmorphic disorder)
Oncologist	Fear of cancer
Genitourinary specialist	Fear of HIV
Neurologist	OCD associated with Tourette's syndrome
Obstetrician	OCD during pregnancy or puerperium
Gynaecologist	Vaginal discomfort from douching

Box 1: Most common symptoms of obsessive-compulsive disorder**Obsessions**

- Fear of causing harm to someone else
- Fear of harm coming to self
- Fear of contamination
- Need for symmetry or exactness
- Sexual and religious obsessions
- Fear of behaving unacceptably
- Fear of making a mistake

Compulsions*Behaviours*

- Cleaning
- Handwashing
- Checking
- Ordering and arranging
- Hoarding
- Asking for reassurance

Mental acts

- Counting
- Repeating words silently
- Ruminations
- "Neutralising" thoughts

Box 2: ICD-10 definition of obsessive-compulsive disorder

- Either obsessions or compulsions (or both) present on most days for a period of at least two weeks
- Obsessions (thoughts, images, or ideas) and compulsions share the following features, all of which must be present:
 - Acknowledged as originating in the mind of the patient
 - Repetitive and unpleasant; at least one recognised as excessive or unreasonable
 - At least one must be unsuccessfully resisted (although resistance may be minimal in some cases)
 - Carrying out the obsessive thought or compulsive act is not intrinsically pleasurable

distressing). Compulsions are repetitive stereotyped behaviours or mental acts driven by rules that must be applied rigidly. They are often intended to neutralise anxiety provoked by the obsessions (fig 1). They are not inherently enjoyable and do not result in the completion of any useful task. To qualify for the diagnosis, the symptoms must be disabling. Even among children, in whom diagnostic criteria allow less insight, most patients acknowledge the senselessness of the thoughts and behaviours, as well as the wish to be rid of them. Box 2 summarises the ICD-10 (international classification of diseases, 10th revision) criteria for diagnosing the condition.

Most patients with obsessive-compulsive disorder experience both obsessions and compulsions (box 1). Common obsessions include unrealistic distressing wor-

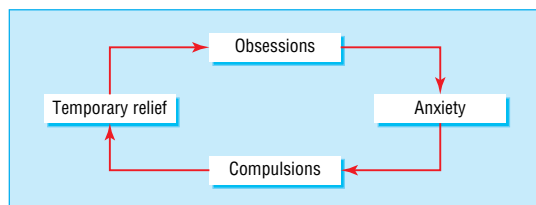


Fig 1 The obsessive-compulsive disorder cycle. Obsessions are intrusive thoughts (ideas, images, or impulses) that repeatedly enter a person's mind against his or her will. These generate considerable anxiety and are difficult to dismiss. Compulsions or rituals are repetitive acts that are performed in an attempt to reduce the anxiety caused by the obsessions, but the relief is only temporary. Later in the course of obsessive-compulsive disorder, rituals can become more automatic and increase, rather than reduce, the anxiety. Psychological theories of obsessive-compulsive disorder suggest that ritualising maintains the problem as it prevents habituation to the anxiety and disconfirmation of the patient's fears. Psychological therapies aim to break this cycle by persuading patients to expose themselves to the feared situations while refraining from performing any rituals; this is known as exposure and response prevention

ries about harm, such as being responsible for an accident or the fear of contamination, accompanied by avoidance of situations in which harm or contamination may occur. These obsessions are linked with compulsive behaviours, which may temporarily reduce the associated anxiety, such as excessive checking or cleaning rituals. Other common obsessions include a need for symmetry or orderliness, often associated with counting, ordering, and arranging compulsions; unwarranted fears and images about committing aggressive or sexual acts; and compulsive hoarding. People of all ages, but especially children, may involve family members in their compulsions or persistently demand reassurance. Excessive doubt, the need for completeness, shame, and abnormal assessment of risk in the mind of the patient are thought to underlie most obsessions.

Aggressive obsessions are common and must be differentiated from violent thoughts occurring in other disorders, such as urges to hurt people in psychopathy. People with pure obsessive-compulsive disorder worry that they might commit an offence but do not carry out the feared act and spend an excessive amount of time and energy resisting and controlling their behaviour to avoid the risk of harm. However, obsessive-compulsive disorder may occur together with other complicating conditions (table 2).⁵ Screening for and treating these comorbidities is an important part of the management.

Can questionnaires help with diagnosis?

Recognition of obsessive-compulsive disorder may require direct questions, as the affected person is often reluctant to volunteer symptoms, particularly if the symptoms are perceived as embarrassing (such as sexual obsessions). People with hoarding symptoms may not see their hoarding as a problem. The recently launched NICE guideline on the treatment of obsessive-compulsive disorder and body dysmorphic disorder recommends six screening questions (derived from the Zohar-Fineberg obsessive compulsive screen; box 3).⁶

Table 2 Conditions that commonly occur with obsessive-compulsive disorder⁵

Condition	Frequency (%)
Depression	50-60
Specific phobia	22
Social phobia	18
Eating disorder	17
Alcohol dependence	14
Panic disorder	12
Tourette's syndrome	7
Schizophrenia	14

Box 3: Quick screen for obsessive-compulsive disorder⁶

- Do you wash or clean a lot?
- Do you check things a lot?
- Is there any thought that keeps bothering you that you would like to get rid of but can't?
- Do your daily activities take a long time to finish?
- Are you concerned about orderliness or symmetry?
- Do these problems trouble you?

Once the diagnosis has been suggested, the use of standardised instruments may help to define the symptom profile, estimate severity and impairment, and monitor response to treatment. A short self completed questionnaire such as the obsessive compulsive inventory may be used.⁷ The current best validated instrument is the Yale-Brown obsessive compulsive scale (Y-BOCS), which exists in both an adult and a child version.^{8,9}

What are the treatments and where should they be accessed?

NICE examined the evidence base supporting the efficacy of all therapies for obsessive-compulsive disorder (and body dysmorphic disorder). In the recently published guideline, NICE recommends a “stepped care” model, with increasing intensity of treatment according to clinical severity and complexity (table 3).⁶ The intention of the guideline is to encourage evidence based treatment to take place at the least intrusive level appropriate to a patient’s needs. In some cases, this means at the primary care level. At the other end of the scale, the guideline supports the establishment of

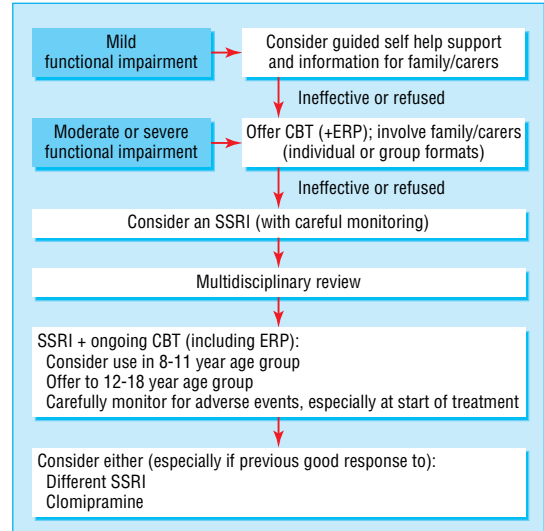


Fig 2 Treatment options for children and young people with obsessive-compulsive disorder. CBT=cognitive behaviour therapy; ERP=exposure and response prevention; SSRI=selective serotonin reuptake inhibitor. (Adapted from NICE guideline⁶)

specialist services for more “difficult to treat” patients. Figures 2 and 3 summarise the treatments for children and adults from the NICE guideline.⁶

The guideline emphasises the importance of better recognition of the disorder across the life span and the need for good information and education. A large variety of resources exist, some of which are summarised in the additional educational resources box. After a diagnosis has been made, the patient and family need to understand the diagnosis and to be helped not to feel blame or shame and the clinician needs to instil optimism about recovery. Guided self help may be effective in early or mild obsessive-compulsive disorder, and both computer and paper self help manuals exist, although fewer options are

Unanswered research questions in obsessive-compulsive disorder (OCD)

Nosological status of OCD

- Should OCD be classified as an anxiety disorder?
- Do subtypes exist, each with different causes (for example, early onset OCD, OCD with comorbid tics, compulsive hoarding)?
- Are hypochondriasis, body dysmorphic disorder, and other “spectrum” disorders variants or completely separate disorders?

Causative factors

- What are the precise genetics of OCD?
- Might environmental factors such as family environment or streptococcal infection be risk factors?

Management questions

- Would screening, with earlier detection and treatment, improve outcomes?
- What is the most effective cognitive behaviour therapy package in terms of intensity and length of treatment and training of therapist?
- How effective is self help, computer guided therapy, or telephone therapy, compared with conventional face to face therapy?
- Does an effective course of cognitive behaviour therapy help to prolong remission and prevent relapse?
- How effective are combinations of cognitive behaviour therapy and drugs in children and adults
- For how long should drugs be used?
- What makes some cases treatment resistant? How might treatments be best modified for these cases?
- Cost effectiveness studies

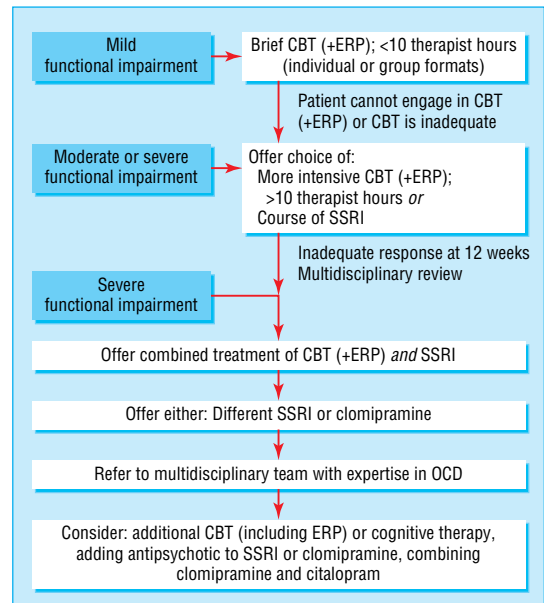


Fig 3 Treatment options for adults with obsessive-compulsive disorder (OCD). CBT=cognitive behaviour therapy; ERP=exposure and response prevention; SSRI=selective serotonin reuptake inhibitor. (Adapted from NICE guideline⁶)

Table 3 NICE stepped care model for obsessive-compulsive disorder (OCD)⁶

Step	Who is responsible for care?		Type of OCD	What is the focus?
	Adults	Children		
1	Individuals, public organisations, national health service		Awareness and recognition	Provide, seek, and share information
2	General practitioners, practice nurses, school health advisers, health visitors, general health settings	CAMHS tier 1	Recognition and assessment	Detect, educate, and discuss treatment options. Signpost voluntary support agencies. Refer if necessary
3	General practitioners, primary care team, primary care mental health workers, family support team	CAMHS tier 1	Management and initial treatment	Assess, review, and discuss options. For adults: brief individual or group CBT (including ERP) with self help materials, SSRI, or consider combined treatments. For children: guided self help, CBT (including ERP)
4	Multidisciplinary care in primary or secondary care	CAMHS tier 2 or 3	Management of OCD with comorbidity or poor response to treatment	Assess, review, and discuss options. CBT (including ERP), SSRI, consider alternative SSRI, combined treatments, or clomipramine
5	Multidisciplinary care with specific expertise in OCD	CAMHS tier 3 or 4	Management of OCD with significant comorbidity, more severely impaired functioning and/or treatment resistance, relapse	Reassess and discuss options. As above, and consider augmentation strategies, admission
6	Inpatient care or intensive treatment programmes	CAMHS tier 4	OCD with risk to life, severe self neglect, or severe distress or disability	Reassess, discuss options, and care coordination. As above, and consider admission or special living arrangements

CAMHS=child and adolescent mental health services; CBT=cognitive behaviour therapy; ERP=exposure and response prevention; NICE=National Institute for Health and Clinical Excellence; SSRI=selective serotonin reuptake inhibitor.

available for the younger age group. NICE paid particular attention to patients' choices in directing treatment and to the careful estimation of risks and the costs of treating or not treating the disorder.

What happens in cognitive behaviour therapy?

NICE reviewed 17 trials in adults and concluded that cognitive behaviour therapy was an efficacious treatment for obsessive-compulsive disorder.⁶ The best randomised controlled trials in the younger age group showed that delivering cognitive behaviour therapy within a family setting was highly effective.¹⁰

In both adults and children, the specific psychological technique most strongly associated with good outcome in studies of cognitive behaviour therapy is exposure and response prevention, which has response rates of up to 85% in patients who complete the therapy.¹¹ The patient generates a hierarchy of feared situations and then practises facing the fear (exposure), while monitoring the anxiety and experiencing that it lessens without the need to carry out a ritual (response prevention). Engaging the person by helping them to design a graded programme of exposure and response prevention, and working collaboratively on easiest challenges first, is essential. Careful education about mechanisms of anxiety, understanding that repeated exposure leads to reduced anxiety, as well as reduction in obsessions, is important for success. Practice is needed, as patients will have been reinforcing their behaviours by avoiding feared situations or carrying out rituals to deal with their fears for some time.

The cognitive model of obsessive-compulsive disorder emphasises remedying faulty reasoning that may have developed with the disorder. Increasingly, therapists use cognitive strategies in combination with exposure and response prevention. Cognitive approaches encourage patients to re-evaluate over-valued beliefs about risk or personal responsibility, to regain a more realistic perspective, and to carry out "behavioural experiments" to test the validity of their beliefs.¹² Whether the addition of cognitive techniques significantly improves the efficacy of exposure and response prevention is as yet unclear.

No evidence exists to support the efficacy of psychodynamic psychotherapy in OCD. NICE therefore does not recommend its use.⁶

Additional educational resources

Information and self help books for children and adults

Wagner A. *Up and down the worry hill: a children's book about obsessive compulsive disorder and its treatment*. New York: Lighthouse Press, 2002—An illustrated book designed to help parents and professionals to explain obsessive-compulsive disorder to younger children through the story of "Casey," a young boy with the disorder

Wever C, Phillips N. *The secret problem*. Sydney: Shrink-Rap Press, 1996—A cartoon book that describes obsessive-compulsive disorder in clear and simple language to help children, teenagers, and parents to understand it and its treatment

Hyman B, Pedrick C. *The OCD workbook: your guide to breaking free from obsessive-compulsive disorder*. Oakland, CA: New Harbinger Publications, 2005—A self help manual for adults and older adolescents, which guides the patient through exposure with response prevention; includes advice for family members

Veale D, Willson R. *Overcoming obsessive compulsive disorder*. London: Constable & Robinson, 2005—A self help book suitable for adults and older teenagers

Schwartz JM. *Brain lock: free yourself from obsessive compulsive behaviour*. New York: Harper Collins, 1997—A self treatment manual suitable for adults and older adolescents

Information for practitioners

March J, Mulle K. *OCD in children and adolescents: a cognitive-behavioural treatment manual*. New York: Guilford Press, 1998—A manualised approach to cognitive behavioural therapy, including psychoeducational material and questionnaires

Clark DA. *Cognitive behavioural therapy for OCD*. New York: Guilford Press, 2003—Overview of cognitive and behavioural techniques

Fineberg N, Marazziti D, Stein DJ, eds. *Obsessive compulsive disorder: a practical guide*. London: Martin Dunitz, 2001

Websites

South London and Maudsley NHS Trust (www.ocdyouth.info)—Information on obsessive-compulsive disorder and how to recover, for young people and their carers

OCD Action (www.ocdaction.org.uk)—National charity in the UK; provides information and support

Obsessive Compulsive Foundation (www.ocfoundation.org)—US national charity

National Institute for Health and Clinical Excellence (www.nice.org.uk/page.aspx?o=cg031&c=mental)—NICE guideline on obsessive-compulsive disorder

Patient's story: teenager with moderately severe obsessive-compulsive disorder

By the time she was 13, Chloe had spent almost a year becoming more and more disabled by troublesome worries and repetitive behaviours. Chloe was worried that she was "going crazy" and did not tell anyone about her symptoms. She had previously been a bubbly, outgoing girl, who was enthusiastic about school and had many friends. She was now late for school every day, and some days she did not go at all. She rarely saw her friends. Her mother noticed unusual behaviours, such as checking. Checks included plugs and the gas cooker, her school bag repeatedly in the mornings, and that her pet dogs were each shut in separate rooms of the house. Chloe was also worried, tearful, and not sleeping well. She was able to explain to her mother that her mind seemed full of terrible, repetitive thoughts that bad things might happen to her dogs or to her family. Carrying out the checks or asking repeated questions made it feel like these bad things would not happen.

Chloe saw her general practitioner, who diagnosed obsessive-compulsive disorder and also wondered if Chloe was depressed. He referred her to child and adolescent mental health services. The diagnosis was confirmed, and Chloe began cognitive behaviour therapy with a nurse therapist, who worked jointly between the general practitioner and the mental health services. After eight sessions, Chloe had made a few gains, cutting back on some of her checking. She was still low in mood, not attending school, and largely housebound, as she thought her dogs would die if she did not check them every few minutes.

A referral was made to a specialist obsessive-compulsive disorder service, where Chloe was reassessed. In a structured interview, Chloe scored in the moderately severe range, and her clinical presentation revealed ongoing impairing obsessive-compulsive disorder as well as moderate depression. Chloe and her mother had read about drug treatment and were keen to try this. Fluoxetine was prescribed (because Chloe had depression as well). After six weeks on fluoxetine, Chloe's mood was noticeably improved. She was also less anxious and agreed to embark on another course of cognitive behaviour therapy involving exposure and response prevention. With her therapist, Chloe worked out a detailed programme of cutting back on time consuming rituals, challenging the anxious beliefs, and learning to tolerate some anxiety, while discovering that nothing bad happened if she did not carry out her ritual. After 12 sessions of therapy, Chloe had only minimal symptoms and was back at school and going out with friends.

Over the next year, Chloe had brief review appointments every three to four months. She requested an extra appointment during a time when symptoms threatened to come back, just after she had been mugged near her home. A "top-up" session of cognitive behaviour therapy enabled Chloe to renew her skills and prevent rituals or avoidant behaviour returning. Nine months after this, Chloe remained well and wanted to try reducing and stopping her fluoxetine. This was gradually reduced and stopped over three months. Chloe has remained well.

Do drug treatments work, and who should get them?

Obsessive-compulsive disorder responds specifically to drugs that inhibit the synaptic reuptake of serotonin—that is, the tricyclic antidepressant clomipramine and the more highly selective serotonin reuptake inhibitors (SSRIs). SSRIs are effective at all ages. Both the effect size and side effect profiles seem to be similar across the life span.¹³

All the SSRIs have been subject to large scale clinical trials (33 in adults, 18 in children).^{14 15} Dose finding studies have been carried out only in adults. Higher doses of SSRIs than those used for depression may be needed to effectively treat obsessive-compulsive disorder.

SSRIs have largely superseded clomipramine for treating obsessive-compulsive disorder because of their lesser toxicity in overdose and more favourable side effect profile. This is especially important for children, in whom cardiac toxicity may be a risk. Head to head

studies show equivalent efficacy and better tolerability for SSRIs relative to clomipramine.¹⁶ Clomipramine remains a useful option but is usually reserved for patients in whom trials of SSRIs have been ineffective.

The therapeutic response to drug treatment in obsessive-compulsive disorder increases gradually over weeks and months; studies show that the benefits continue to accrue for at least six months and probably longer. Patients should be warned that side effects such as nausea and agitation tend to emerge early, often before the therapeutic response is consolidated, but usually abate. A trial of at least 12 weeks at the maximum tolerated dose is advisable before effectiveness is judged.

Several studies have shown that people with obsessive-compulsive disorder continue to benefit from long term drug treatment and that a large number relapse if the drug is discontinued or switched to placebo under trial conditions.¹⁷ Possibly, patients with greater comorbidity are at most risk of relapse. For at least some cases, therefore, treatment may need to be continued indefinitely.

Drugs, psychological therapies, or both?

On the available evidence, for children, adolescents, and adults, psychological and drug treatments seem to be equally effective. According to NICE guidance, cognitive behaviour therapy is recommended as the first line treatment for children and adolescents, because of the assumption that it has fewer risks than SSRIs.⁶ For adults, cognitive behaviour therapy or pharmacotherapy can be offered first. Currently, in the United Kingdom, provision of evidence based psychological therapies, such as cognitive behaviour therapy, is inadequate, and expansion of these services is needed.¹⁸

Uncertainty remains as to whether the two forms of treatment combined are superior to psychological or drug monotherapy. Several studies in adults have looked at this; some suggest that addition of drugs increases the efficacy of cognitive behaviour therapy, whereas others show no additional benefit. In a recent trial in young people, a placebo pill was compared with sertraline alone, cognitive behaviour therapy alone, and cognitive behaviour therapy plus sertraline. All three active treatments were better than placebo and not significantly different from each other.¹⁹ Cognitive behaviour therapy, either alone or in combination with drug treatment, might help to prolong remission and prevent relapse on discontinuation of the drug, but this remains to be tested in long term studies.

Do additional treatments help?

Up to 40% of patients who present to psychiatrists fail to respond adequately to either cognitive behaviour therapy, drugs, or a combination of the two. Careful reassessment with detection and treatment of related problems may improve outcomes. For example, young people with developmental difficulties on the autism spectrum may be susceptible to obsessive-compulsive disorder as teenagers or young adults, and these patients may need specifically tailored cognitive behaviour therapy packages.

Some evidence exists to support various drug strategies in resistant cases, including increasing the dose of the SSRI to the maximum tolerated dose and switching to an alternative, as response may be idiosyncratic. SSRI and clomipramine have been combined in some

studies; this needs careful monitoring and should be done in a specialist setting. Obsessive-compulsive disorder does not respond to antipsychotic drugs given as monotherapy. Evidence from children and adults shows that adding first generation and second generation antipsychotics, in low dose, to SSRIs may benefit resistant cases and obsessive-compulsive disorder with comorbid tics.²⁰ This intervention should be initiated by specialists in obsessive-compulsive disorder and monitored closely for effectiveness and side effects.

Can further research help us?

Debate is ongoing about whether obsessive-compulsive disorder is appropriately classified as an anxiety disorder. Research studies in a range of modalities (neuropsychological, neuroimaging, genetics, psychopharmacology) suggest that the disorder has a heritability and neurobiology distinct from the other anxiety disorders.²¹ Whether or not obsessive-compulsive disorder has a distinct neurobiology, it is highly responsive to psychological treatments that involve cognitive and behavioural modification of anxiety symptoms.

Altered functioning of specific brain regions (basal ganglia and orbitofrontal cortex) is implicated in the disorder. Evidence for this includes high rates of obsessive-compulsive disorder in diseases that affect these brain regions, such as Tourette's syndrome, Huntington's chorea, and Sydenham's chorea. A fluctuating form of obsessive-compulsive disorder, tics, or both (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection—PANDAS) has been recently described and is thought to be secondary to streptococcal infection and mediated by autoantibodies binding to basal ganglia.²² Furthermore, research into subtypes, such as compulsive hoarding, have suggested that neurobiologically distinct forms of obsessive-compulsive disorder may exist.²³⁻²⁵ Research is also needed on early environmental and family risk factors that may, in complex interaction with genes, be implicated in the genesis of the disorder.

Several disorders seem to be related to obsessive-compulsive disorder, either by the nature of their symptoms, which show similarities to obsessions or compulsions, or by their frequent co-occurrence. These have been termed obsessive-compulsive disorder spectrum disorders (box 4),²⁶ although whether all of these disorders are causally related to obsessive-compulsive disorder is unclear. Hypochondriasis involving a preoccupation with health related fears can be similar to the disorder. Body dysmorphic disorder, which involves obsessional thoughts relating to imagined or slight defects in appearance and frequent checking in the mirror, can also be difficult to distinguish from obsessive-compulsive disorder.

Box 4: Conditions related to obsessive-compulsive disorder²⁶

Body dysmorphic disorder (dysmorphophobia)
Trichotillomania
Hypochondriasis
Anorexia nervosa
Gilles de la Tourette's syndrome

The classification of obsessive-compulsive disorder remains an area of active debate and research, as does the search for causes (see unanswered research questions box). Identification of meaningful subgroups may lead to the development of tailored treatments, especially for those patients who do not respond to existing strategies.

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Competing interests: NAF has done consultancy work for Lundbeck, GlaxoSmithKline, Astra-Zeneca, and Bristol-Myers Squibb; is a speakers' bureau member for Astra-Zeneca and Wyeth; and has received educational support from Janssen, Wyeth, and Cephalon. IH and DM-C: none declared.

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