



“REVIEW ON OCD: INTRODUCTION, CLINICAL PRESENTATION, EPIDEMIOLOGY, CASE PRESENTATION, RISK FACTORS, PSYCHOTHERAPY.”

Syed Zakir¹, Tabish Nisar², Santosh Kumar Tripathi³, Rajesh Kumari Patil^{4*}

^{1,2}Department of Pharmacy Practice (Student), Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda,

³Professor and Clinical Psychologist, Department of Psychiatry, Adesh Institute of Medical Sciences and Research, Adesh University, Bathinda.

⁴Professor, Department of Pharmacy Practice, Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda,

* **Corresponding Author:** Rajesh Kumari Patil

*Professor & HOD, Department of Pharmacy Practice, Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda. Email: rkpatil3014@gmail.com

Abstract:

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder characterized by obsession and compulsions. The WHO has classified OCD as one of the 10 most handicapping conditions by lost income and decreased quality of life. OCD once was believed a rare disorder, but epidemiologic studies revealed it affected between 2% and 3% of total world-wide population. Although several effective treatments are currently available for OCD that will be psychiatric or pharmacological, most patients do not seek treatment until the disorder is seriously affecting their lives. Cognitive behavioral psychotherapy (CBT) is the psychotherapy/ treatment for children, juvenile and grownups with OCD. CBT helps create an internal tactic for battling OCD that will give lifelong benefit for the patient. Individuals respond differently to psychotherapy, fair as they do to medication. CBT is moderately free of side-effects, but all patients possess some anxiety throughout treatment.

Keywords: Obsessive compulsive disorder (OCD), Obsession, Compulsions, Serotonin, serotonin reuptake inhibitors (SSRI'S), Cognitive behavioral therapy (CBT).

Introduction:

Obsessive-compulsive disorder is an anxiety disorder characterized by unreasonable thoughts and fears (obsessions) that lead you to do repetitive behaviors (compulsions). It causes significant loss in social or job-related functioning. Patient with OCD display a great variability of symptoms on presentation to clinicians. The variety and peculiarity of symptoms that apparent can obscure accurate

judgement and interruption in proper treatment of the disorders. Patients can be confidential about their symptoms and do not report them.

OCD presents itself in many appearances, and people are often surprised to learn that it goes far beyond the common perception of excessive. Obsessions are persistent unwanted thoughts, mental images or urges that generate feelings of anxiety, disgust or discomfort. Compulsions are repeated actions or routines that occur in reply to obsessions to achieve a relief from anxiety. Compulsions occur often and typically take-up at least one hour per day, impairing one’s quality of life. Compulsions cause relief in the moment, but cause obsessions to grow over time due to the repeated reward-seeking behavior of completing the ritual of relief. Many adults with OCD are conscious that their compulsions do not make any logic, but they still perform them to relieve the distress caused by obsessions.

OCD is a major mental health distress, next level of disability, and disruption of the persons social and occupational functioning. The WHO has classified OCD as one of the 10 most handicapping condition by lost income and decreased quality of life.

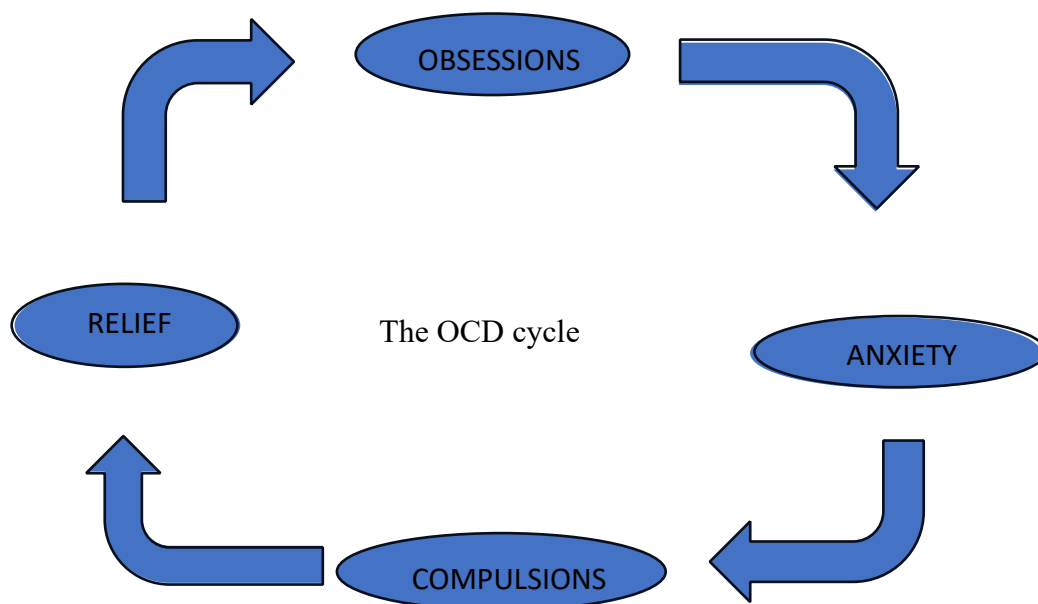
Clinical Presentation:

Obsession:

- Recurrent thoughts (e.g., feeling dirty after touching an article, suspicious whether the stove/oven was turned off).
- Repetitive image (e.g., recurring sexually clear pictures).
- Repetitive urges (for instance., necessity for symmetry or putting things in definite order).
- Worries that you have not locked the gate and switch the oven/stove off and so on.
- Dread of missing material or not possessing things you might want.

Compulsions:

- Repetitive activities (e.g., hand washing, checking, ordering, need to task, need to confess).
- Recurrent mental acts (for instance., counting, repeating words soundlessly, praying).
- Clean hand until the hand is raw.
- Repeatedly checking of the gate to confirm it is locked.
- Recurrently scrutinize loved ones to confirm that they are safe.
- Arranging objects in a particular order, such as books, bedsheets and so on.



Epidemiology:

OCD once was believed to be a rare disorder, but epidemiologic studies revealed it affects between 2% and 3% of total world-wide population. The overall lifetime prevalence is slightly higher in women, but men tend to have an earlier onset of illness (between ages 20 and 29 years). Many patients report having mild symptoms, for years before full OCD emerges, and an estimated one third to one half of patients have onset during childhood or adolescence. Prepubertal OCD is three times more common in boys than in girls. Women with OCD often have onset or worsening of OCD during pregnancy, regardless of sex, the severity of illness usually worsens during stressful life periods.

Although several effective treatments are currently available for OCD, most patients do not seek treatment until the disorder is seriously affecting their lives. One study found OCD patients waited an average of 7.5 years after the onset of OCD before seeking medical evaluation for their disorder. This may be because most OCD patients realize their symptoms are senseless, so they attempt to hide their disorder because of embarrassment. People with OCD often carry out their rituals privately and may be very successful at concealing their symptoms from others. Initial treatment for OCD is commonly sought outside psychiatric settings, and the obsessive-compulsive symptoms are often missed.

The general public and health care professionals need to recognize that OCD is a biological disorder for which effective treatments are available. Four simple questions are recommended for screening for potential OCD. Do you have to wash your hands over and over? Do you have to check things repeatedly? Do you have recurrent distressing thoughts you cannot get rid of? Do you have to complete actions again and again or in a certain way? Clinicians in a variety of healthcare settings can incorporate these screening questions into their practice to use, when possible, signs of OCD are present. Healthcare providers should be prepared to provide education about the nature and treatability of OCD to suspected sufferers and to make appropriate treatment referrals in these cases

Case Presentation:

Question 1: N.G. is 25-year-old woman whose husband complains she spends 2 hours a day cleaning the stove and takes five (5) showers each day. The unusual behaviour began about 1 year ago after the birth of their son but has continued to worsen, and N.G.'s husband states that he cannot deal with her “odd habits” any longer. N.G. recently lost her job as secretary because of tardiness (it took her 3 hours to get ready for work) and spending too much time away from her desk in the ladies’ room. N.G. admits that it is silly, but she has irresistible urges to make sure both she and her surroundings are completely free of germs so her child will not get sick. She also confines herself to one floor of their three-level house because she is afraid, she will fall down the stairs while carrying her son. N.G. also states that she constantly has “what if” thoughts about horrible things happening to her family, which are very disturbing. The physician’s diagnosis is OCD. What clinical features of OCD does N.G. display, and how can her symptoms be objectively evaluated?

N.G. displays many characteristic symptoms of OCD. The most commonly encountered clinical presentation of OCD involves excessive fear of contamination with dirt, germs, or toxins and repeated washing of hands or cleaning objects or surroundings. These persons also avoid touching possibly dirty objects (e.g. doorknobs, money) or shaking hands with people. Another common clinical presentation of OCD is the patient with pathological doubt who constantly worries something bad will happen because of his or her negligence. Individuals can be scared they have failed to lock the gate, turn off the oven, shut the fridge door, or secure the medicine cabinet from children. As a result, they endlessly check and recheck their activities.

N.G displays obsessions of contamination and pathological doubt, and compulsions of excessive cleaning and washing. These symptoms are time-consuming, cause significant anguish, and have led to her job loss and

marital problems. As seen in this case, most person present with a mixture of various obsessions and compulsions. N.G also realize her thoughts and behaviors are “silly”, which most often is the case of

OCD. This case also illustrates the onset of OCD during times of stressful or significant life events. Pregnancy, death of relative, and marital discord has been identified as precipitating factor in the onset of OCD.

The aforementioned Y-BOCS is a beneficial instrument in the initial assessment of those who present with symptoms of OCD and may be used in the objective assessment of N.G.’s symptoms. The Y-BOCS is a 10-item scale with a maximal possible score of 40; a score of more than 15 is generally considered to represent clinically significant obsessive-compulsive symptoms. This scale is standard tool for evaluating drug efficacy in OCD clinical trials and is often used in clinical practice to assess response to treatment. Other OCD assessments instruments include the National Institute of Mental Health Obsessive-Compulsive Scale, the Leyton obsessional inventory, and the self-rated Maudsley obsessional-compulsive Inventory. Special versions for use in children have been developed for the Y-BOCS and Leyton obsessional-compulsive Inventory.

Question No. 2: On assessment, N.G.’s Y-BOCS score is found to be 33. Her physician prescribes fluoxetine and instruct N.G. to take 100mg every morning for 1 week and then 200 mg every morning thereafter. He also refers N.G. to a psychologist to receive CBT. Is this initial choice of therapy appropriate?

SSRIS such as fluoxetine are considered the best choice of primary pharmacotherapy for OCD. The primary differences between SSRIs involve pharmacokinetic properties and potential for drug interaction. Because there is no overall differences in efficacy among the four SSRIs approved for OCD, Fluoxetine is a suitable selection for N.G. however, the prescribed dosing instructions for N.G. are not appropriate. The initial recommended dosage for Fluoxetine in adult is 50mg/day (25mg in children), and is best taken in evening because it tends to be sedating. Using higher-than necessary dosage can increase both adverse effects and medication costs, and these factors can lead to early termination of therapy. The dosage can be increased by 50-mg increment every 3 to 4 days according to patient tolerability, up to the initial targeted dose of 200 mg/day and maximum of 300mg/day. Daily doses exceeding 100mg should be given in two divided doses if once-daily dosing is not well tolerated.

The decision to include Cognitive Behavioral Therapy in N.G.’s treatment plan is appropriate. The overall efficacy of these nonpharmacologic treatments is estimated to be 50% to 70% when used alone, and their use to complement pharmacotherapy is considered vital. N.G.’s Y-BOCS score is 33 indicates a moderate-to-severe symptom severity, which provide further support for using a combined treatment approach. For N.G., exposure plus response prevention therapy might involve covering her hands with dirt and not allowing her to wash them for a certain time period. These behavioral techniques cause extreme nervousness and worry, which frequently lead to dropout from therapy or noncompliance with “homework assignment” but are highly effective if the patient can adhere to treatment.

Question NO. 3: What patient counselling information should be provided to N.G. in conjunction with the prescribed treatment?

All OCD patients beginning treatment should be counseled that medication response occurs gradually and several weeks may elapse before beneficial effect becomes noticeable. It is necessary to emphasize that maximum response may take 4 months or longer and complete eradication of all symptoms is unlikely. It also is helpful to point out that a variety of other medications exist for those who do not respond adequately to an initial trail.

N.G. should be educated about possible Fluoxetine side effects, include nausea, sedation or insomnia, and headache. Medication should be taken with food to decline these effects. Side effects are most common during initial weeks of therapy, are usually dose related, and often subside with continued treatment. Other aspects of SSRI therapy, including supplementary adverse effects and their supervision and drug-drug interactions. Patients should be fortified to account any problems to their treatment provider. The importance of adhering to prescribed therapies, both pharmacologic and behavioral, should also be stressed.

Question No. 4: After 4 weeks, N.G. is taking fluoxetine 200 mg daily and bearing the medication well. She grumbles and has not noticed much improvement, and her Y-BOCS score is slightly decreased at 30. N.G. has been to cognitive behavioral therapist twice but is reluctant to return because the therapy was so stressful. N.G. requests to be transferred to a more effective medication, and also asks to be given some alprazolam to help calm her nervousness during behavioral therapy sessions. What is the best course of action for N.G. at this point?

Switching to alternative medication is not recommended at this point because not adequate time has elapsed to assess fluoxetine’s efficiency. N.G. is tolerating Fluoxetine well and has shown a mild improvement, so this medication should be continued for at least another 4 weeks. Extra counselling should be given to N.G. to emphasize the gradual response to treatment in OCD. An increase in Fluoxetine dosage, up to 250 or 300 mg/day, may be considered after several more weeks because some patients may respond better to higher dosage. If N.G.’s symptoms continue to cause significant functional impairment after 10 to 12 weeks of higher-dose Fluoxetine therapy, a change in treatment will be indicated.

N.G. should be encouraged to continue cognitive behavioral therapy to optimize the change for successful treatment. An anxiety response is integral to the therapeutic benefit of behavioral therapies; because benzodiazepines can blunt this response, they may reduce their efficacy. Therefore, alprazolam should be avoided, and temporary reduction in the intensity of behavioral therapy may be indicated instead. Fluoxetine can also inhibit the CYP3A4-mediated metabolism of alprazolam, resulting in more pronounced effect from given dose.

Question No. 5; After 5 months of treatment, N.G. is happy to report her OCD is much improved (Y-BOCS score of 12). She still has intermittent obsessions related to contamination and doubting, but they are less intense than before. She is usually able to resist urges to clean and wash excessively and is using the stairs in their home with only mild discomfort. Her previous employer has agreed to let her return to her secretarial position when she is ready, and plan to do so soon. N.G.’s husband is extremely pleased with her progress. Their key question at this visit is whether treatment can be obsolete now because N.G. is doing so well. What recommendation should be provided regarding the long-term course of therapy for N.G.?

This case illustrates a common outcome of OCD treatment, in which some symptoms persist, but significant improvements in functioning occur. It is presently suggested that effective treatment for OCD may be continued.

Risk-Factors:

The cause of OCD is mysterious. Together environmental and genetic factors are supposed to play a character. Various risk factors rise the probabilities of developing the disorder.

- **Genetic:** studies have shown that having a first-degree relative (parent or sibling) with OCD is associated with an increased chances of developing the disorder. Researchers have not recognized any one genetic factor or set of genes that absolutely leads to OCD, but studies discovering the linking between genetic and OCD are ongoing.
- **Biology:** Brain imagining studies have shown that people with OCD often have differences in the frontal cortex and subcortical structure of the brain, area of the brain that impact the ability to control behaviour and emotional responses. Study is in progress to well understand the link between OCD symptoms and parts of the brain. This information can aid researcher develop and adapt treatments targeted to definite brain locations.
- **Temperament:** Some research has found that people who exhibit more reserved behaviors, experience negative emotions, and show symptoms of anxiety and depression as children are more likely to develop OCD.
- **Childhood trauma:** Some studies have reported an association between childhood trauma and obsessive-compulsive symptoms. Further research is needed to know this bond.

- Drugs: Some medication and other drugs, such as methamphetamine or cocaine can induce OCD in people without previous symptoms.

Some atypical antipsychotics (second-line antipsychotics) such as olanzapine and clozapine can induce OCD in people, particularly individuals with schizophrenia.

- Environment: OCD may be more common in people who have been bullied, abused or neglected and it sometimes starts after a significant life event, such as childbirth or bereavement. It has been reported in some studies that there is a connection between child-head trauma and obsessive-compulsive symptoms. Extra research is required to understand this bond well.

Psychotherapy:

Cognitive behavioural psychotherapy (CBT) is the psychotherapeutic treatment of choice for kids, teenagers, and grownups with OCD. CBT helps the patient create an interior tactic for battling OCD that will be of all-time benefit.

What Is CBT? The “BT” in CBT stands for behaviour therapy. Behaviour therapy helps people learn to change their thoughts and feelings by first changing their behaviour. Behaviour treatment for OCD includes exposure and response prevention (ERP).

- Exposure is based on the fact that anxiety usually goes down after long enough contact with something feared. Thus, people with obsessions about microbes are told to stay in contact with “germy” substances (e.g., handling money) until their nervousness is extinguished. The person’s anxiety tends to decline after repetitive exposure until he/she no longer fears the contact. • For exposure to be of the most help, it needs to be combined with response or ritual prevention (RP). In RP, the person’s rituals or avoidance behaviours are jammed or prevented. For instance, those with extreme qualms about microbes must not only stay in contact with “germy things,” but must also refrain from ritualized washing.
- Exposure is generally more helpful in decreasing anxiety and obsessions, while response prevention is more helpful in decreasing compulsive behaviours. Despite years of struggling with OCD symptoms, several persons have astonishingly slight difficulty tolerating ERP once they get started.
- One key to successful CBT is in starting with symptoms that cause somewhat less anxiety than the most bothersome symptoms. In this way, somebody doing CBT can learn the methods and learn how to diminish his nervousness without starting with the very hardest problems first.
- Cognitive therapy (CT) is the other component in CBT. CT is frequently added to ERP to aid diminish the disastrous thinking and overstated sense of responsibility often seen in those with OCD. For example, a juvenile with OCD may have faith in that his failure to remind his mother to wear a seat belt will cause her to die that day in a car accident. CT can help him encounter the faulty assumptions in this obsession. Armed with this proof, he will be better able to engage in ERP, for example, by not calling her duty to make sure she reaches safely.
- Other techniques, such as thought stopping and distraction (suppressing or “switching off” OCD symptoms), satiation (prolonged listening to an obsession usually using a closed-loop audiotape), habit reversal (replacing an OCD ritual with a similar but non-OCD behaviour), and contingency management (using rewards and costs as incentives for ritual prevention) may sometimes be helpful but are generally less effective than standard CBT.

People respond in a different way to psychotherapy, just as they do to medication. CBT is comparatively free of side effects, but all patients will have some nervousness throughout treatment. CBT can be separate (you and your doctor), cluster (with other people), or family. A doctor may provide both CBT and medication, or a psychologist or social worker may provide CBT. Irrespective of their specialties, those treating you should possess sound knowledge about the treatment of OCD and eager to cooperate in providing your care.

How To Get the Maximum Outcomes of Psychotherapy

- Keep your appointments.
- Be honest and open.
- Do the homework assigned to you as part of your therapy.
- Follow up the therapist feedback on how the treatment is working.

How successful is CBT? About 25% of patients refuse psychotherapy/CBT, those patients who complete it report a 50%-80% decrease in OCD symptoms after 12-20 sessions. Patients with OCD who respond to CBT generally stay well, often for years to come. When someone is being treated with medicine, using CBT with the medicine may help prevent relapse when the medicine is stopped.

How long does CBT take to work? When given on a weekly basis, CBT may take 2 months or more to display its complete effects. Intensive CBT, which comprises 2-3 hours of therapist-assisted ERP daily for 3 weeks, is the fastest treatment offered for OCD.

What is the best setting for CBT? Maximum OCD patients do good with weekly CBT, in which they practice in the office with the therapist once a week and then do everyday ERP at home. Homework is compulsory because the situations or objects that cause OCD are exclusive to the individual's environment and often cannot be replicated in the therapist's office. In intensive CBT, the therapist may come to the patient's home or workplace to conduct ERP sessions. In very rare cases, when OCD is severe, CBT is best conducted in a hospital setting.

References:

1. Pharmacotherapy, A pathophysiologic approach. Ninth edition
2. Wikipedia. obsessive-compulsive disorder. {online}. <https://en.m.wikipedia.org/wiki/obsessive%20%80%93compulsive-disorder>. Retrieved on 01-jan-2024.
3. Google scholar. OCD. Suicidality in obsessive compulsive disorder [OCD]: a systematic review and meta-analysis. {online}. <https://www.sciencedirect.com/science/article/abs/pii/S0272735815000434>.
4. The National Institute of Mental Health (NIMH) (January 2016). “What is obsessive compulsive disorder (OCD)?” {online}. <https://www.nimh.nih.gov/health/topics/obsessivecompulsive-disorder-ocd>.
5. Diagnostic and statistical manual of mental disorder. Fifth edition. DSM 5. American psychiatric publishing 2013.
6. Alevizos B, Papageorgiou C, Christodoulou GN (September 2004). "Obsessive-compulsive symptoms with olanzapine". *The International Journal of Neuropsychopharmacology*. Page no.: 375–377.
7. Kulkarni G, Narayanaswamy JC, Math SB (1 January 2012). "Olanzapine induced de-novo obsessive compulsive disorder in a patient with schizophrenia". *Indian Journal of Pharmacology*. Page no.: 649–650. Robbins, T. W., Vaghi, M. M. & Banca, P. Obsessive compulsive disorder: puzzles and prospects. *Neuron* **102**, 27–47 (2019).
8. Bloch, M. H., Landeros-Weisenberger, A., Rosario, M. C., Pittenger, C. & Leckman, J. F. Meta-analysis of the symptom structure of obsessive-compulsive disorder. *Am. J. Psychiatry* **165**, 1532–1542 (2008). {online}. [https://www.cell.com/neuron/fulltext/S08966273\(19\)30073-X?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS089662731930073X%3Fshowall%3Dtrue](https://www.cell.com/neuron/fulltext/S08966273(19)30073-X?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS089662731930073X%3Fshowall%3Dtrue)
9. Stein, D. J., Hollander, E. & Josephson, S. C. Serotonin reuptake blockers for the treatment of obsessional jealousy. *J. Clin. Psychiatry* **55**, 30–33 (1994). {online} <https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.2008.08020320>

10. Monzani, B., Rijdsdijk, F., Harris, J. & Mataix-Cols, D. The structure of genetic and environmental risk factors for dimensional representations of DSM-5 obsessive-compulsive spectrum disorders. *JAMA Psychiatry* **71**, 182–189 (2014).
11. Ruscio, A. M., Stein, D. J., Chiu, W. T. & Kessler, R. C. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol. Psychiatry* **15**, 53–63 (2008). **This community survey provides data on the prevalence and comorbidity of OCD in the general population.** <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1792141>
12. Brander, G., Pérez-Vigil, A., Larsson, H. & Mataix-Cols, D. Systematic review of environmental risk factors for obsessive-compulsive disorder: a proposed roadmap from association to causation. *Neurosci. Biobehav. Rev.* **65**, 36–62 (2016). <https://www.nature.com/articles/mp200894>
13. Dykshoorn, K. L. Trauma-related obsessive-compulsive disorder: a review. *Health Psychol. Behav. Med.* **2**, 517–528 (2014). <https://www.sciencedirect.com/science/article/abs/pii/S0149763415302293?via%3Dihub>
14. Salkovskis, P. M. Obsessional-compulsive problems: a cognitive-behavioural analysis. *Behav. Res. Ther.* **23**, 571–583 (1985). <https://www.tandfonline.com/doi/full/10.1080/21642850.2014.905207>
15. Benzina, N., Mallet, L., Burguière, E., N’Diaye, K. & Pelissolo, A. Cognitive dysfunction in obsessive-compulsive disorder. *Curr. Psychiatry Rep.* **18**, 80 (2016). <https://www.sciencedirect.com/science/article/abs/pii/S0005796785901056?via%3Dihub>
16. Goodman, W. K. et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch. Gen. Psychiatry* **46**, 1006–1011 (1989). **The Y-BOCS remains the gold standard measure for assessing symptom severity in OCD.** <https://link.springer.com/article/10.1007/s11920-016-0720-3>
17. Rosario-Campos, M. C. et al. The Dimensional Yale–Brown Obsessive–Compulsive Scale (DY-BOCS): an instrument for assessing obsessive–compulsive symptom dimensions. *Mol. Psychiatry* **11**, 495–504 (2006). <https://jamanetwork.com/journals/jamapsychiatry/articleabstract/494743>
18. Huppert, J. D. & Franklin, M. E. Cognitive behavioural therapy for obsessive-compulsive disorder: an update. *Curr. Psychiatry Rep.* **7**, 268–273 (2005). <https://www.nature.com/articles/4001798>
19. Huppert, J. D. & Franklin, M. E. Cognitive behavioural therapy for obsessive-compulsive disorder: an update. *Curr. Psychiatry Rep.* **7**, 268–273 (2005). {online}. <https://link.springer.com/article/10.1007/s11920-005-0080-x>
20. Hirschtritt, M. E., Bloch, M. H. & Mathews, C. A. Obsessive-compulsive disorder. *JAMA* **317**, 1358 (2017). {online}. <https://jamanetwork.com/journals/jama/article-abstract/2614194>
21. Wootton, B. M. Remote cognitive–behaviour therapy for obsessive–compulsive symptoms: a meta-analysis. *Clin. Psychol. Rev.* **43**, 103–113 (2016). {online}. <https://www.sciencedirect.com/science/article/abs/pii/S0272735815001361?via%3Dihub>
22. Skapinakis, P. et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* **3**, 730–739 (2016). {online}. [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(16\)30069-4/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(16)30069-4/fulltext)