Current Pharmacological Treatments for Obsessive-Compulsive Disorder

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Introduction

Obsessive-Compulsive Disorder (OCD) is a severe, chronic condition that affects 2% to 3% of the United States population, or 4 million to 7 million people.[1] The illness is characterized by recurrent thoughts, images, feelings, or behaviors that persist against the patient's wishes to suppress them and are usually accompanied by marked anxiety. These symptoms are often associated with marked impairment of function.[2] OCD affects people regardless their cultural background or socio-economic status.[3] **OCD was listed as the tenth leading cause of disability worldwide by a recent World Health Organization study.** The total cost of the disorder in the US is estimated to be more than $8 billion.[4] **OCD is a treatable condition with 50% to 60% of patients responding to first line of treatment, which includes pharmacological and/or psychological intervention.[5,6] However, about one-third of the patients improve only partially, and roughly 20% do not respond to conventional treatment strategies.[7]** The situation is complicated by the fact that many health professionals are not educated about the appropriate treatments that can be offered to OCD patients.[8]

This review summarizes the available literature on the pharmacological treatments of OCD. We discuss the factors affecting the treatment choices for this disorder. We discuss tolerability, side effects, dosing, and the safety of medications used in the treatment of OCD. In addition, management of partial response to medications is reviewed, and the available interventions for refractory OCD are considered. Finally, while we will not be reviewing extensively the psychological treatments of OCD, we will discuss the interplay between the therapeutic and pharmacological interventions that can be used to maximize the treatment.

The Expert Consensus Guidelines on the treatment of obsessive-compulsive disorder, published in 1997, provided the first guidance for clinicians on the management of this often-vexing condition.[9] Several recent reviews are available on the subject of the treatment of OCD.[10,11] Our review focuses on a practical approach to the treatment of OCD with front-line medications and

psychotherapeutic interventions as well as treatment of resistant cases.

Factors Affecting Treatment

The decision to administer treatment for a particular patient usually requires the clinician to analyze multiple factors. These include the presence of a diagnosis of OCD or OCD Spectrum disorders and comorbid conditions, interplay of biological, genetic, and psychological factors, and the stage of the disorder. The clinician also has to balance available data, from experience and literature, on efficacy, pharmacodynamics, and side effects of particular medications. If several medications are used, drug interactions need to be considered.

Diagnosis and Assessment:

Diagnosis of OCD frequently presents difficulty. DSM IV calls for the presence of recurrent and persistent thoughts, images, or impulses that are perceived by a person as their own and that are causing anxiety or distress (obsessions) and actions or rituals aimed at reducing the anxiety (compulsions) (Table 1).[12] **In fact, the OCD picture can be far more complex with mental rituals, reassurances, avoidances, and covert behaviors, which do not easily fit into the category of obsessions or compulsions.** OCD is one of the most complex mental illnesses. If we consider the main assessment tool for OCD, the *Yale Brown Obsessive Compulsive Scale* (Y-BOCS),[13] and specifically the *Y-BOCS Checklist*, which lists most of known obsessions and compulsions, we find that it consists of more than 60 different types of symptoms. There have been attempts to cluster these symptoms together.[14,15] **Principal component analysis has revealed an existence of five main types of OCD.[15] They include:**

- **violent/aggressive**
- **images/checkers**
- **contamination fears/washers**
- **symmetry and exactness/arrangers**
- **hoarders/savers.**

However, some of the patients' presentations do not fit into these clusters. Diagnosis can be even more complicated due to the existence of OCD Spectrum disorders or disorders that mimic OCD, in that the main presentation of these disorders is the repetitive actions or behaviors.[16,17] In addition, a variety of neurological conditions and personality disorders, including Obsessive Compulsive Personality Disorder (OCPD) and other anxiety disorders, could be confused with OCD.[18,19] It is understandable that with the presence of such a variety of syndromes with similar features the screening for this disorder is difficult. **Initial 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?"*) often lead to overdiagnosing OCD.** This problem resulted in the exclusion of OCD from most of the recent epidemiological surveys.

A Multi-faceted, Evolving Process:

The clinician who wants to assess this disorder should not simply look for the presence of obsessions and compulsions, but rather understand the condition as a multifaceted, evolving process that starts with initial anxieties and fears, and faulty coping strategies that lead to perpetuating the fears and behaviors (Table

Table 1

DSM-IV Criteria for Obsessive-Compulsive Disorder

1. Obsessions and/or compulsions
2. recognized as excessive or unreasonable
3. Causes marked distress, time-consuming (> 1 hour/day), or interferes with functioning
4. Content not due to another Axis I disorder
5. Not due to a substance or general medical condition

2). **The disorder typically starts with an initial fright or gradually increasing anxiety (of contamination, for example).** The person attempts to eliminate anxiety by worrying about the source in an attempt to analyze and solve the problem. Initially, this strategy helps as it would for any normal person to eliminate or decrease anxiety and fear (e.g., *"Germs are probably dead"*). **However, because the specific thinking patterns of OCD require an absolute, fault-proof solution that is impossible (*"What if they are not dead?"*), the worry persists and becomes obsession or anxious, uncontrollable worry.** The persistence of anxiety calls for more active coping strategies. As a result, the person takes certain actions that could eliminate or suppress fears and obsessions (e.g., washing). Washing initially eliminates or reduces the fear of contamination. However, since absolute assurance of safety is impossible in OCD patients, they keep repeating the compulsive ritual invariably retriggering fears. Usually this ritual continues until the patient gives up. Giving up also initially helps to reduce anxiety, but as it leads to the eventual decrease or elimination of certain normal activities (such as washing or showering), or causes delay in beginning normal activities or lateness, usually the end result is further deterioration in functioning. The pressures associated with functional impairment lead to even more stress and anxiety, translating into more fear and rekindling the vicious cycle of OCD, frequently leading to despair and depression. **It is important for a clinician to understand this progressive development of OCD symptoms because patients in different stages may respond differentially to medications or to behavioral therapy, which I will discuss later.**

Table 2

INTERPLAY BETWEEN ANXIETY AND OCD SYMPTOMS

Stages of OCD	Fear and Anxiety
1. Initial stress and anxiety	▲
2. Worry, thinking, problem solving	▼
3. Obsessions	▲
4. Initial compulsions (including mental)	▼
5. Extensive compulsions	▲
6. Abandonment of Compulsions (withdrawl)	▼
7. Avoidance	▼ then ▲
8. Depression	▲

Comorbid Conditions:

Another important factor governing the treatment is the presence of comorbid psychiatric conditions, which are not infrequent in OCD.[20] **It is especially important to consider the presence of other anxiety disorders, such as *s*ocial anxiety disorder, frequently overlooked in OCD, that can affect the functional improvement of the patients.[21] Mood disorders including major depression and bipolar disorder are very important for administration of both pharmacological and psychological treatments.[22] The presence of Posttraumatic Stress Disorder (PTSD) is also frequently overlooked and needs to be assessed.[23]** In our OCD Treatment-resistant Program, approximately one-quarter of the patients can trace the onset of their OCD to some traumatic or very stressful event in their lives.[24]

Biological Mechanisms:

Biological mechanisms responsible for the vicious cycles in OCD are not fully understood.[25] However, OCD is one of the few disorders for which we have some idea of what neuroanatomical circuits participate in psychopathology.[26] As we explained above, two processes are likely to participate in OCD. The first is related to fear and anxiety formation

and emotional regulation, and the second is specific cognitive processes that include information processing of the threat, decision-making, and facilitation of thoughts and behaviors. Limbic circuits that are usually thought to regulate the fear formation and other emotional responses include amygdala, cingulum hypocampal and parahypocampal, and some orbital and temporal cortical areas.[27] **Some of the studies of OCD patients reveal abnormalities in these circuits, specifically in cingulum.[28] However, most of the neuroanatomical studies using neuroimaging and other techniques indicate the presence of abnormalities in cortico-stiriato-thalamic-cortical circuits that seem to have a broad function of modulating and coordinating emotional and cognitive processes in humans.[29-31]** Impairment in these circuits, caused by either a neurological condition (strokes, Tourette's syndrome and Huntington's disorder) or autoimmune disorders such as Sydenham's chorea frequently have OCD-like symptoms.[32]

Neurochemically, OCD has been most associated with the serotonergic system.[33] Results of studies of static measures of serotonergic function in obsessive-compulsive disorder have, however, been inconsistent, and other work has focused on more informative dynamic measures.[34,35] For example, administration of the serotonin (5-HT_2) agonist m-chlorophenylpiperazine (mCPP) has been accompanied by exacerbation of obsessive-compulsive disorder symptoms and a blunted neuroendocrine response.[36] After treatment with a serotonin reuptake inhibitor, behavioral and neuroendocrine responses to mCPP seem to be normal.[37] This work leads to questions about the role of specific 5-HT subreceptors in obsessive-compulsive disorder. **Effects of mCPP on the postsynaptic 5-HT2C receptor may be especially relevant in OCD.[38] Pre-clinical and clinical data also suggest that the 5-HT1D terminal autoreceptor plays an important part; desensitization of this receptor in the orbitofrontal cortex needs high duration and high dose administration of serotonin reuptake inhibitors.[39]** Preliminary challenge, pharmacological, genetic, and imaging data lend support to a role for the 5-HT1B and 1D receptors in obsessive-compulsive disorder.[40,41]

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.[42] Another neurotransmitter system that could be especially important in mediation of obsessive-compulsive disorder in some patients is dopamine.[43] In pre-clinical studies, administration of dopamine agonists leads to stereotypic behavior, whereas in human beings such agents can exacerbate symptoms and tics of obsessive-compulsive disorder. Conversely, **dopamine blockers, such as haloperidol, are used in treatment of Tourette's syndrome, one of the spectrum of obsessive-compulsive disorders.[44] Furthermore, augmentation of serotonin reuptake inhibitors with such agents can be useful in treatment-refractory obsessive-compulsive disorder.[45]** It seems that dopamine and serotonin systems maintain a sort of balance with each other and many other systems, including glutamate neurotransmission, some neuropeptides, and gonadal steroids that all may be playing a part.[46-50] Ultimately, the role of second and third messenger pathways in obsessive-compulsive disorder will need to be explored.

Interplay of Biological, Genetic, and Psychological Factors

It is important to understand the psychopathology of OCD as interplay of biological, genetic, and psychological factors.

Recent family, twin, and other genetic studies indicate that at least **some types of OCD can be transmitted possibly in autosomal dominant or recessive fashion**.[51] Patients who are genetically vulnerable to OCD usually develop their symptoms very early, between eight and 14 years of age, often without the presence of major stressors.[51] Different hypotheses exist on what exactly is transmitted, mostly

focusing on components of the serotonergic system.[52,53] Some genetic theories focus on neuroimmunology or genetic vulnerability to autoimmune reactions.[54] **Early reports of an association between obsessive-compulsive disorder and Sydenham's chorea were confirmed** in a systematic investigation leading to consideration of whether some cases of obsessive-compulsive disorder resulted from autoimmune processes that disrupted cortico-striatal-thalamic-cortical circuits.[55] **A syndrome of autoimmune neuropsychiatric disorder associated with streptococcal infections, or PANDAS, has been proposed to describe children who have acute onset of obsessive-compulsive disorder symptoms with or without tics after streptococcal infection.[56] In patients with PANDAS, their obsessive-compulsive disorder and tic symptoms respond to immunomodulatory interventions such as plasma exchange and intravenous immunoglobulin.[57] 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.[58]** In some studies, 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.[59]

Biological assaults on the brain and specifically lesions in orbito-frontal-cortico-striato-thalamic circuits are also capable of producing OCD symptoms.[60] These includes strokes, head injuries, illicit drug use, and brain infections such as encephalitis. Strong traumatic events have been described to lead to OCD in patients without any known biological or genetic predisposition.[61] In the majority of adult patients, by the time they reach treatment, their clinical picture invariably represents a mixture of biological and psychological factors. Early onset of OCD creates and perpetuates stress by disrupting the social, family, and work or school function of the patients. This frequently forces them to miss normal developmental stages; this generates additional stress, which in turn worsens their OCD.[62]

Knowing the factors described above can help the clinician to make appropriate choices regarding the treatment of patients suffering from OCD.

Pharmacological Treatment

General Principals of Pharmacological Treatment for OCD:

It is important to be aware of the specific difficulties of the pharmacological management of OCD patients. **Treatment of an OCD patient is often difficult because of the specific attitude this population has about taking medication.** OCD patients, by nature of their illness, have an inflated need for control and are suspicious and doubtful. Taking medication presents these patients with a sensation of loss of control. Both a patient and a psychopharmacologist need to pay attention to these feelings to be able to assure compliance. On the other hand, some patients with OCD are prone to develop a magical thinking toward a medication and believe that a particular medication may cure them, only to become disappointed later on. Early discussion of realistic expectations regarding the effectiveness of the medication will help to solve this problem. Another problem that may occur with this population is that medication may become a part of the patient's ritual. Some patients can take medication only on certain days, in certain numbers of pills, or have fears associated with the color, name, or "chemical purity" of the pill. Also, while the majority of OCD patients are not prone to develop side effects, a subgroup of somatically and environmentally concerned OCD patients may exhibit difficulty swallowing pills or multiple somatic symptoms. It is very important to assess early in the treatment whether any of the patient's fears or rituals interfere with compliance. We recommend initially to see those patients frequently and to provide them with good access to a clinician for possible discussion of the problems associated

with the beginning of the treatment. Sometimes it is even permissible to yield to rituals and to reassure the patient in order to preserve the collaboration and compliance in the initial stages of the treatment. The last principle is that a psychopharmacologist needs to be aware of new scientific developments in the field of OCD and of psychological and alternative treatments. This group of patients frequently does their "homework" by thoroughly investigating the Internet and other informational resources and, absence of knowledge on the part of the clinician, raises their level of suspiciousness. We recommend, if possible, collaborating with a psychologist or other trained therapist who has training in Cognitive-Behavioral Treatment for OCD. Providing the patient with comprehensive treatment may improve both compliance and outcome.

The treatment of OCD patients usually proceeds as a step-by-step approach, which is briefly listed in Table 3.

Serotonin-Reuptake Inhibitors:

Serotonin-reuptake inhibitors, or SRIs, have been considered the first line of drug treatment for OCD.[63] SRIs, or agents that inhibit the reuptake of serotonin back into the nerve terminal, were introduced in late 1980s and early 1990s for the treatment of depression and almost immediately began to be used in OCD. At the present time, each of five selective SRIs (*fluoxetine* [Prozac], *paroxetine* [Paxil], *fluvoxamine* [Luvox], *sertraline* [Zoloft], and *citalopram* [Celexa]) have shown efficacy for OCD in randomized controlled trials.[64-68] Although antidepressants without this serotonergic action have occasionally been described as effective in small, uncontrolled studies and case reports, possibly because they alleviated comorbid depression, controlled head-to-head comparisons have consistently shown them to be less efficacious than SRIs.[69,70] It is not clear why SRIs work in OCD. Earlier theories proposed that OCD is caused by a decreased serotonin neurotransmission improved by SRIs.[71] This introduces faulty logic that may lead one to believe that a fever may be caused by aspirin insufficiency in the body. In fact, neurochemical and neuroendocrinological studies have *not* led to a coherent etiologic model of serotonin dysfunction in OCD.[72] Recent theories suggest that SRIs, through their effect on serotonin neurotransmission, modulate dysfunctional neural circuits, possibly changing a balance between several neurotransmitters.[72,73] SRIs quickly became the first choice of medicational treatment of OCD because of their efficacy, tolerability, and safety.[66,67] As yet, we have no predictors based on symptom patterns or on side effect profiles to guide SRI choice.[74]

The best assumption, at the current state of science, is that the SRIs all are equivalent in terms of efficacy. The meta-analyses of randomized placebo-controlled trials to date have all found little difference in efficacy among them.[74,75] **In the majority of studies, 40% to 60% of patients were "much" or "very much" improved on clinical global impression ratings. Complete response is unusual, and most patients have some residual symptoms. Patients who do not respond to an initial SRI are less likely to respond to subsequent ones, but further trials are worthwhile.**[76] Usually it is recommended to try at least two, or occasionally three, SRIs before switching to a different class of drug.[9]

Dosing and Initiation of the Treatment

Recommended dosing levels are detailed in Table 4. For elderly patients, and for anyone who has a history of sensitivity to medication or is anxious about side effects, starting with a low dose (e.g., 10 mg of *paroxetine* or *fluoxetine,* or 25 mg of sertraline) and increasing it more slowly than usual (e.g., raising it every 10 to 14 days instead of every five to seven days) is best. Hasty dose increases are usually unnecessary and can be counterproductive. We recommend continuing to increase the dose if no change in anxiety and affective symptoms occur to the maximum tolerated (or until the upper limit for that drug is reached). If anxiety, worry, or

Table 3

CURRENT ALGORITHM FOR THE TREATMENT OF OCD

1. The first step in the treatment of Obsessive-Compulsive disorder is to administer either medications or cognitive behavioral therapy.If drug treatment is to be used, it is advisable to start with an SSRI.

2. If there is no response, or the SRI is not tolerated, another SRI should be used with or without psychological treatment. The SSRI should be tried in an appropriate dose for at least six weeks.

The patient may be considered treatment resistant. Subsequent steps are much more obscure, and very little research exists to guide us through the process. The treatment choice is ususally guided by physician experience, familiarity with medications, and side effects. Patient knowledge and preferences also play a major role. A psychiatrist should guide treatment.

3. If there is no response, the ususal recommendation is to try another SSRI (under some circumstances all five of them may be tried) or switch to clomipramine.

4. If there is parital response to SRIs, augmentation strategies can be attempted. These usually include buspiron, lithium, clonazepam or a novel neuroleptic.

5. If the response is inadequate, or there is no response despite following steps 1 through 4, SNRIs such as venlafaxine, nefazadone, or mitrazapine may be tried ususally with an SSRI orsome other form of pharmacological augmentation.

The patient may be considered "treatment refractory." Treatment at this stage should mostly be conducted by a specialized OCD center or with guidance from such a center.

6. Treatment in a specialized program usually include intensive behavior modifications administered in outpatient, partial hospital, inpatient units, or residential facilities.

7. Stimulants, tricyclics, MAOIs, or ECT could be considered as the next step, but these strategies have low rate of response.

8. Experimental pharmacological strategies such as such as intravenous clomipramine or weekly oral morphine could be tried.

9. Non-pharmacological experimental strategies could be considered, such as Transcranial Magnetic Stimulation (TMS), Deep Brain Stimulation (DBS), or Vagus Nerve Stimulation (VNS). Efficacy and parameters of these treatments still remain to be explored.

10. Finally, if symptoms remain severe and incapacitating, patients may consider neurosurgery. This may be considered right after step 7, bypassing experiemental treatments.

obsessive thinking is reduced, the dose increase may be stopped, and the physician may wait until week six of the treatment when outcome should be reassessed and a further dose increase proposed if necessary. Specific attention should be given to fluoxetine, which became a primary agent on many formularies since it is available in generic form. *Fluoxetine has the longest half-life, and blood levels of the drug may continue to rise for another two weeks following the dose adjustment.*

Most patients do not experience benefit in reducing obsessive-compulsive symptoms before six weeks, and at least six weeks at the maximum tolerated dose is required for an adequate therapeutic trial.[63] The most effective dose is often (but not always) higher than that used for depression, and patients may well respond to higher doses when lower ones have failed. The majority of the studies demonstrated that **maximum benefit usually occurs by the twelfth week of treatment.** Improvement may continue for several months after the initial response, and **lasting benefit is seen with long-term continuation in responders.[77]**

Start treatment with a low dose of an SRI that

you are most familiar with and that is the least expensive on the patient's insurance formulary. Increase the dose once a week to a mid-range dose, or as tolerated, and wait till week six of the treatment before gradually increasing the dose to maximum, or as tolerated, over the next two to four weeks. If patient has no response or low tolerance, switch to another SRI. If there is a 30% decrease in symptoms and the dose is at maximum and well tolerated, begin augmentation. If the patient does not respond to two SRIs, you can add or switch

Table 4

Recommended Dosing Regimen and Side Effect Profile of SRIs

Medication	Dose (OCD) mg	Half-life (with metabolites)	Drug Interaction	Side Effects[+]	Advantage/Difference	Management Comments
Citalopram	20 – 120	35	low	Sx ◆ SE ◆◆ Ins 0 Wt ◆	Mostly specific SRI Kidney metabolism Does not affect sleep	Good for elderly and medically ill due to low drug interaction. Can be used in liver impaired (alcoholics?)
Clomipramine	25 – 300	32	high	Sx ◆◆◆ SE ◆◆◆ Ins 0 Wt ◆◆◆	Best in obsessional thoughts Sleep inducing, stops diarrhea; Affects many neurotransmitter systems and could be more effective in some cases.	Needs blood level monitoring (and tri-cyclics); problematic in elderly and ill, specifically with liver or heart problems. Beware of seizures.
Fluoxetine	20 – 120	92 +	mod	Sx ◆◆ SE ◆ Ins ◆ Wt ◆◆	Cheapest and longest existing SRI. Because of long half-life gives little withdrawl. Good safety record including pregnancy. Most activating SRI	Watch out for drug interactions. May be in patient's blood three to four weeks after discontinuation
Fiuvoxamine	50 – 600	14	high	Sx ◆ SE ◆◆◆ Ins 0 Wt ◆◆	Most short acting SRI, sedates at night, least likely to cause activation or agitation. 3A4 metabolism (different drug interaction from other SRI)	Some advantage in combination with clomipramine due to metabolism. Good efficacy in panic and OCD
Paroxetine	20 – 120	16	high	Sx ◆◆◆ SE ◆◆◆ Ins ◆ Wt ◆◆◆	Some norepinephrine reuptake Very effective in a variety of anxiety symptoms (known to PCP) Convenient in use (usually no tiration)	Strongest withdrawl Negative publicity Side effects Problematic in elderly and ill
Sertraline	25 – 400	62 +	low	Sx ◆◆◆ SE ◆ Ins ◆◆ Wt ◆◆	Second most activating Low drug interaction Some dopamine activity Needs titration	Good in medically ill due to low drug interaction

[+]Side effects: Sx = sexual SE = sedation Ins = insomnia Wt = weight gain

Table 5

Recommended Dosing Regimen and Side Effect Profile of Other Medications

Medication	Dose (OCD) mg	Half-life (with metabolites)	Drug Interaction	Side Effects[+]	Advantage/Difference	Management Comments
Venlaflaxine	25 – 450	16	low	Sx ◆ SE ◆◆ Ins ◆ Wt ◆	SNRI (blocks Norepinefrine Reuptake)	Good for elderly and medically ill due to low drug interaction. Good efficacy in many anxiety disorders. Needs titration
Mirtazapine	7.5 – 45	30	mod	Sx ◆ SE ◆◆◆◆ Ins 0 Wt ◆◆◆◆	NE reuptake blocker; Serotonin 5HT2 and 3 receptor agonist	Sedative agent in elderly Rapid weight gain In larger doses actually activate
Nefazadone	100 – 400	4	mod	Sx 0 SE ◆◆◆ Ins 0 Wt 0	NE reuptake blocker Serotonin 5Ht2 receptor agonist; short acting	Liver test monitoring is needed; sedative agent in elderly, can provoke anxiety in some patients
Trazadone	50 – 300	7	mod	Sx 0 SE ◆◆◆ Ins 0 Wt 0	Serotonin 5Ht2 receptor agonist	Sedative agent in elderly Short acting; can provoke anxiety in some patients. Marginally effective in depression
Valproate	250 – 1000	8	mod	Sx ◆ SE ◆◆ Ins 0 Wt ◆◆◆	GABA-ergic AE drug Liver metabolism	Needs blood levels, ammonia levels monitoring; slow titration and withdrawl
Gabapentin	100 – 3600	6	low	Sx 0 SE ◆◆ Ins 0 Wt ◆	GABA-ergic AE drug Kidney metabolizes	Slow titration and withdrawl; seizures possible with rapid withdrawl
Clonazepam	0.5 – 8	16	mod	Sx ◆ SE ◆◆ Ins 0 Wt 0	Benzodiazepine Long-acting	Slow titration and withdrawl; seizures possible with rapid withdrawl
Lorazepam	0.5 – 8	8	low	Sx ◆ SE ◆◆ Ins 0 Wt 0	Benzodiazepine Long-acting	Slow titration and withdrawl; seizures possible with rapid withdrawl; dependency forming

[+]Side effects: Sx = sexual SE = sedation Ins = insomnia Wt = weight gain

to clomipramine. On occasions, one or two trials of other SRIs could be justified.

Side-Effects Management

Management of pharmacological intervention and side effects in OCD patients should be performed very carefully and throughout the treatment. Although side-effect rates differ slightly among the SRIs, the majority of patients are able to tolerate all of these medications.[78] The side effects and other properties of SRIs that can assist with the treatment choice are summarized in Table 4. **SRIs are very safe medications for almost all OCD patients except for those with severe hepatic or renal impairment.** They are generally safe in overdose.[79] However, most SRIs significantly inhibit various isoenzymes of the cytochrome P450 system, which is central to the hepatic metabolism of many commonly used drugs.[80] By this mechanism, **they can increase blood levels of all tricyclic antidepressants (including clomipramine), many antipsychotics (including clozapine, thioridazine, haloperidol, and risperidone), beta-blockers, opiates, and several antiarrhythmics (type 1C). *Citalopram* only weakly inhibits cytochrome P450 and usually is preferred in cases where drug interaction is of concern.**[81]

Gastrointestinal disturbance is common. However, it normally subsides within a few days and can be reduced by taking the medication with the main meal of the day, at night, or together with an antacid. The last method may, however, interfere with drug absorption. **Hyperactivity and an increase in anxiety, nervousness, and agitation are also common but usually abate within the first two weeks of treatment.** These SRI-induced symptoms are less frequent in OCD patients than in other anxiety disorder patients. However, patients need to be informed of the possibility of increased anxiety, and those who develop it need to be seen once a week through the first two weeks of the treatment. **Four of the side effects that, once started, usually persist through the treatment are sexual difficulties, sedation, weight gain, and insomnia.**[82] They are the most frequent reasons for premature discontinuation of the medication several months into the treatment. Sexual side effects, ranging from delayed orgasm to anorgasmia to complete loss of libido, are very common with SRIs. They occur in 20% to 40% of patients taking these medications. Brief drug holidays or dose reduction for a few days before sexual activity may be effective, except in the case of fluoxetine, which has a long half-life. Coadministration of *buspirone* (Buspar), *bupropion* (Wellbutrin), *mirtazapine* (Remeron), *trazodone* (Desyrel), stimulants, and *sildenafil* (Viagra) was helpful in case reports but no definitive treatment is available for this problem.[83] Other side effects include *Serotonin Syndrome* when SRIs are combined with other drugs that enhance serotonergic neurotransmission (especially monoamine-oxidase inhibitors [MAOIs]). Moreover, care is needed when switching agents, particularly switching from fluoxetine—again, because of its long half-life.[79] While SRIs appear to be non-teratogenic and safe in the neonatal period, they have been shown to be quite effective and are preferable during pregnancy.[84] The decision of continuing or stopping SRIs during pregnancy is a difficult, one and risks and benefits should be thoroughly discussed with the patient.

Treatment Course and Discontinuation

The duration of the treatment is usually indefinite since **relapse occurs in 80% to 90% of patients upon full discontinuation.**[77] Early discussion of the chronic course of OCD may help to ameliorate anxiety associated with long-term medication use. If discontinuation is desirable, it should be gradual and slow for all SRIs except fluoxetine in order to avoid a discontinuation reaction.[85] With fluoxetine, some patients are able to tolerate more rapid withdrawal without much problem. Such reactions are characterized by anxiety, dizziness, insomnia, irritability, fin-like symptoms, feelings of detachment, and sensations resembling elec-

tric shocks. **Withdrawal from paroxetine seems to carry the greatest risk because of its short half-life. Symptoms are usually self-limiting and are rapidly relieved by reinstating the drug or by switching to another SRI with longer half-life.** Occasionally, very slow reductions may be required over several weeks even with fluoxetine. Concurrent competent cognitive behavioral therapy may reduce relapse rate and assist discontinuation, but this remains to be confirmed in randomized trials.

Clomipramine:

When two SRIs have failed to improve OCD symptoms, the next logical step is a trial of *clomipramine* (Anafranil). **It is a tricyclic antidepressant with strong SRI properties. Clomipramine may either be added to an SRI, in patients with partial response, or used instead of SRIs.** Clomipramine was actually the first antiobsessive medication introduced to the US market.[86] Early trials demonstrated its considerable efficacy of clomipramine. More than 35% of the patients were nearly symptom free and more than 60% of patients experienced significant improvement in their symptoms, while only a few patients improved on placebo. However, due to an unfavorable side-effect profile and cumbersome monitoring, SRIs quickly replaced clomipramine as a first choice medication for OCD.[64,65]

Clomipramine may be slightly more effective than SRIs. Greist and coworkers conducted a meta-analysis of four large multicenter, randomized controlled trials comparing *clomipramine*, *fluoxetine*, *sertraline*, and *fluvoxamine* with placebo.[74] **They found an approximately 66% chance of improvement with anyone of the SRIs compared to an 83% chance with clomipramine.** Similarly, Piccinelli and coworkers' meta-analysis of 47 randomized controlled trials conducted in Europe found a 61% reduction in *Yale-Brown Obsessive-Compulsive Scale* (Y-BOCS) scores with clomipramine compared to a 22% to 28% reduction with the same three SRIs.[75] In contrast, head-to-head comparisons have not shown clomipramine to be superior to SRIs.[87-89] However, most of these trials had methodological flaws and biased design. Thus, the comparative studies to date are inconclusive; and large, well-conducted trials are required to confirm or refute the findings of meta-analyses of placebo-controlled trials. ***Clomipramine* and its metabolite desmethyl-clomipramine affect, to some degree, norepinephrine and dopaminergic system as do most of the tricyclics, which may explain the different degree of efficacy.** While the relationship of norepinephrine and dopamine reuptake blocking properties to antiobsessive efficacy is doubtful, it may relate to additional decrease in anxiety and depression causing overall greater improvement of the patient.

Safety, Tolerability, and Side Effects

Clomipramine affects histamine and many other receptors and, as a result, has more side effects than do the SRIs.[87] On the contrary, in meta-analytic studies dropout rates with clomipramine were significantly lower than with SRIs.[74,75] Rasmussen has suggested that in early trials there was no effective alternative to clomipramine, so patients were more likely to persist with treatment.[90] In comparative studies in which clomipramine was started at the recommended dose of 25 mg, dropout rates were comparable to those of SRIs.[87-89] So although more likely to cause side effects, clomipramine, if prescribed correctly and titrated slowly, seems to be tolerated almost as well as SRIs. **Clomipramine can also cause fatal cardiac arrhythmias in overdose and should not be prescribed to patients with a significant suicidal risk. It should also be avoided in patients with cardiac instability, particularly if conduction defects are present, and should be used with caution in persons at risk for urinary retention and those with narrow-angle glaucoma or significant hepatic or renal impairment.** Sedative, anticholinergic (e.g., dry mouth, constipation) and antiadrenergic

(e.g., postural hypotension) effects are common. When combination with SRIs, neuroleptics, or other medications is indicated, this should be done carefully with knowledge of additive effects and drug interactions. **Clomipramine treatment alone or in combination with other medications should be done only under careful blood level and ECG monitoring.** This monitoring should be started with a baseline assessment and followed initially by monthly blood levels and bimonthly EEG and afterwards by repeated monitoring every six to eight months.

Practical Recommendations

Clomipramine can be added an SRI if no response or partial response to that SRI is observed. This should be done under careful monitoring of ECG, cardiovascular parameters (pulse and blood pressure) and blood levels of clomipramine because of possible pharmacodynamic interaction and toxicity. This is especially important with older or physically compromised people. An SRI can later be tapered off and blood levels of clomipramine rechecked.

Augmentation Strategies in Treatment-resistant OCD

Since 40% to 60% of patients do not respond adequately to SRI or clomipramine treatments, clear strategies are needed for treating those who show partial or little response. At this stage, we are entering initial management of treatment-resistant cases. We strongly recommend, if the patient is being treated by a primary care physicians, a consultation from a psychiatrist who is more familiar with augmentation strategies should be done. Unfortunately, the literature does not offer any well-validated solutions. For patients with severe residual symptoms following an adequate trial of an SRI (i.e., a therapeutic dose for 12 weeks or more with full compliance), several options can be considered. If cognitive behavioral therapy (CBT) has not been tried, it should be offered at this time or at least a consultation with a trained therapist should be sought. The interplay between medication and therapy will be discussed in the next section. If CBT treatment is not available or if it is not feasible because of cost or time constraints, the administration of drug combinations should be tried. Polypharmacy has been widely used in practice and is currently a rule rather than exception for this stage of OCD treatment. However, none of the combined or augmentation strategies summarized briefly below has been conclusively validated in controlled trials.

Venlafaxine (Effexor):

While there are no controlled trials demonstrating the efficacy of venlaflaxine alone in the treatment of OCD, **there are several case reports suggesting that combining SRIs with venlaflaxine, which is also a norepinephrine reuptake blocker, may be helpful.**[91,92] However, combination may be more tolerable, and in contrast to clomipramine, there is very little additional drug interaction. Dose ranges up to 450 mg of venlaflaxine have been used. **Side effects are similar to those of SRIs, specifically in higher doses.**

Clonazepam (Klonopin):

While adding clonazepam may not be desirable at early stages of the treatment because of dependency and withdrawal issues, by this stage of OCD management (which is several months of unsuccessful medicational trials), most of the patients are so needy and desperate that physicians are compelled to institute a benzodiazepine treatment. *Clonazepam* has more evidence for efficacy as an adjunct agent in OCD than do other benzodiazepines.[93] **The advantages of clonazepam include long half-life that permits once-daily use (often before sleep)** and possible serotonergic system upregulation that provides more specific anti-obsessional effect. **Clonazepam is probably ineffec-**

tive when used alone except that it decreases overall anxiety.[94] Side effects may be limiting and include depression, cognitive deficits, irritability, and intoxication. Should not be used "as needed," especially if CBT is instituted.

Atypical Antipsychotics:

Antagonists of both D2 and 5-HT2 receptors have been emerging within the last decade as pivotal treatments for treatment-resistant OCD.[93] In his early reviews, Jenike suggested that conventional neuroleptics have been better than any other agent in the augmentation of the SRIs' effects.[95] Interaction of dopamine and serotonergic systems was proposed as a possible mechanism of action. However, their use was precluded by the possibility of extrapyramidal side effects and tardive diskinesia.

The atypical neuroleptics with additive effect on the serotonergic system are lacking those side effects, at least in lower doses. However, there are reports of these atypical agents exacerbating OCD in patients with comorbid schizophrenia when used alone.[96] Contrary to that, in combination with SRIs they seem to have a therapeutic effect.

Risperidone **(Risperdal) has shown to be effective in open trials and in case series.[97]** In a randomized, controlled trial that was conducted on 36 patients with SRI-refractory OCD,[98] fifty percent of those taking risperidone, but none of those taking placebo, were "much" or "very much" improved on the Clinical Global Impression scale. Two open trials have been conducted using olanzapine (Zyprexa) in patients showing partial response to an SRI.[99,100] Recently, our group conducted a double blind, placebo-controlled trial using olanzapine in 26 patients with OCD; 46% of patients in the olanzapine group showed a response and only 3% showed a response in the placebo group. *Clozapine* has not been investigated as an augmentation agent, but McDougle and colleagues found that none of 10 patients with treatment-refractory OCD responded to clozapine used alone.[101] Given the relative toxicity of this agent, its use in OCD cannot be justified at present. There are ongoing trials with other atypical neuroleptics (e.g., *ziprazadone* [Geodon] and *quitaiapine* [Seroquel]), but no results are available. Approximately 50% of response in very resistant patients is remarkable, and **atypical neuroleptics in combination with an SRI should be considered as one of better ways of management of non-responders to SRI treatment.** The combination of SRIs and atypical antipsychotics is generally well tolerated. **The response tends to occur at lower doses (*risperidone*, two to six mg daily; olanzapine, five to 20 mg daily), and a four-week therapeutic trial at the maximum tolerated dose is considered sufficient.** However, there are some limitations to the use of this combination. SRIs may reduce the breakdown of risperidone and olanzapine and this requires cautious dosing. Additional side effects such as sedation, weight gain, or the possibility of extrapyramidal effects may be troublesome. Moreover, it's not clear which patients respond to this combination. There are some indications those patients with severe, bizarre obsessions, low insight, and tics are less responsive to SRIs alone. For these patients, early addition of atypical neuroleptics may be indicated.

Lithium or Other Mood Stabilizers:

Lithium enhances serotonin transmission and, in combination, may work where SRIs alone failed. However, despite promising case reports, **lithium alone was not efficacious in two double-blind, placebo controlled trials.[102,103]** There is another reason to use lithium or, in fact, other mood stabilizers such as *valproate* or *gabapentin* in this population. **There is emerging data on increased comorbidity with bipolar disorder in treatment-resistant OCD.** In addition, SRIs are capable of causing mood instability and hypomania that could go unnoticed for

a long time. **The dose range of lithium and other agents is similar to that used in mood stabilization** and monitoring of blood levels, and liver, kidney, and other parameters need to be done where appropriate to monitor toxicity.

Other Agents:

Buspirone (BuSpar), a partial 5-HT 1A receptor agonist, has been used for over a decade. Case reports were promising. However, **four controlled trials have yielded disappointing results.**[104] The low toxicity and benign side effect profile made it a popular choice, but the use of buspirone for SRI augmentation is not warranted by either clinical data or by experience. Case reports suggest that this medication can counteract sexual side effects of SRIs and, if confirmed, this may serve as justification for an occasional use of buspirone/SRIs combination.

Many other augmentation strategies and medications or herbal combinations have been used, including l-tryptophan, inositol, *fenfluramine* (Pondimin), *pindolol* (Visken), oxytocin, *trazodone* (Desyrel), and an androgene antagonist. None of these has shown sufficient promise.[105-110]

In summary, begin augmentation with venlaflaxine unless definitive hypersensitivity to SRIs exist. Then add clonazepam or, if there is a history of drug abuse, a GABAergic mood stabilizer such as gabapentin can be added. If there is no response within two to four weeks, a trial of an atypical neuroleptic is warranted. This trial may be followed by an augmentation with buspirone, trazodone, fenfluramine, or l-triptophane, depending on your level of comfort with the drug and the side effect profile of the combination. Behavior therapy should be tried at the same time or in sequence.

Combining CBT with Medication

Cognitive-Behavioral Therapy (CBT) was the first psychotherapy for which careful empirical support was obtained and is a standard treatment for OCD in adults and children.[6] **The most important component of behavioral therapy is Exposure and Response Prevention (ERP).**[111] It consists of confrontation with the feared stimuli combined with prevention of faulty coping behaviors such as compulsions or avoidance. The cognitive component of the treatment or correction of faulty beliefs (including inflated responsibility, over-importance of thoughts, excessive concern about the importance of controlling thoughts, and overestimation of threat) might be less important and probably works only in combination with ERP. Some researchers, however, believe that cognitive approaches are as effective as exposure procedures. *The therapy, just like medications, can effect changes in the brain, specifically in the orbital frontal cortex and striatum.*[112] However, the true mechanism of these changes is unknown. There is the possibility of different targets of CBT versus pharmacological intervention.

Metha-analytic studies have demonstrated that one of predictors of poor response to SRIs is severity of compulsive and avoidant behavior (see stages four through seven in Table 2), **whereas the most noticeable predictor of non-response to CBT is severity of worry and anxiety and an inability to tolerate these strong affects** (see stages one through three in Table 2). It is possible that psychopharmacological interventions cause improvement of anxiety, depression, and obsessiveness while only effecting secondary changes in coping behaviors such as compulsions and avoidance. CBT, on the contrary, modifies coping behaviors and only later causes the resetting of the threshold of anxiety and modification of abnormal thinking. In our OCD Treatment-resistant program, we frequently see patients whose anxiety and obsessive thinking was improved by medications but who considered themselves to be medication non-responders because their com-

pulsions did not improve and who stopped medication for that reason. When CBT was instituted, these patients greatly benefited from a combined approach.

Unfortunately, only a few studies have assessed how best to sequence or combine pharmacotherapy and psychotherapy for obsessive-compulsive disorder with mixed outcome results.[113,114] **In clinical practice, it would seem sensible to routinely encourage patients who receive pharmacological treatment to also understand and adhere to the principles of cognitive-behavioral therapy.** The therapy can be administered individually, in groups, or by self-help computer instruction. 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 is appropriate in some cases. Psychodynamic psychotherapy for obsessive-compulsive disorder is generally ineffective, and there are no data to support its use. However, it can be successfully implemented as an additional therapy when significant personality deficiencies exist.

Management of Treatment-refractory Cases

When both psychological and pharmacological approaches (including adequate trials of each SRI, with and without augmentation) have been unsuccessful, other options must be considered. **It is important at that point to reassess and to review the diagnosis for the presence of any comorbid conditions such as drug dependency, organic conditions, psychosis, or a mood disorder and to explore psychosocial stressors or secondary gain issues that my be participating in maintaining symptoms. We would recommend at that point that a general psychiatrist get a consultation from a clinician specializing in the treatment of OCD.** There is usually a listing of these clinicians available from patient advocacy groups or foundations (e.g., OCD Foundation: www.ocdfoundation.org; Anxiety Disorders Association of America: www.adaa.org). There are many specialty treatment centers for treatment-resistant OCD. These centers can offer a package of intensive cognitive behavior therapy, psychoeducation, family intervention, and pharmacological treatment administered on an inpatient unit, in a partial hospital, or in a residential facility. This treatment is frequently effective even in severe OCD patients that do not respond to any other treatment strategy. Four- and five-year follow up studies are available documenting how improvement acquired in these programs has a tendency to persist.

Psychopharmacological Strategies:

When medication strategies listed in the previous sections are exhausted, non-standard approaches could be used. Monoamine oxidase inhibitors had been used for the treatment of OCD before the introduction of clomipramine and SRIs. A randomized, controlled trial compared phenelzine (Nardil) with clomipramine (Anafranil) and found the two to be equally efficacious.[115] A more recent placebo-controlled comparison of phenelzine with fluoxetine, however, found fluoxetine to be significantly superior except for obsessions regarding symmetry, which responded well to phenelzine.[116]

Traditional antipsychotics also can be tried at this point. **Comorbidity with schizophrenia is common in OCD.**[117] Obsessions and compulsions are surprisingly common in schizophrenia, with studies estimating rates of 8% to 46%. **We suggest that trials of antiobsessional drugs begin only after psychotic symptoms have been stabilized with medication; we also urge caution with respect to drug interaction since many SSRIs increase blood levels of antipsychotics.** In OCD with a comorbid tic disorder that fails to respond to an SRI, the addition of *haloperidol* (Haldol) or *pimozide* (Orap) in doses up to 2 to 10 mg has been associated with higher response rates than would be

expected from changing to another SRI. In these studies, tics were also reduced.[118] Inhibition of excess dopaminergic activity in the basal ganglia via D2 receptor blockade is the putative mechanism of action.

There is some evidence for the efficacy and safety of *intravenous clomipramine*, which may become the optimal strategy in treatment-resistant cases. Researchers have suggested that the ratio of clomipramine to its metabolite desmethylclomipramine (which also inhibits noradrenaline reuptake) is increased with parenteral treatment through reduction of first-pass hepatic metabolism and that this explains the greater tolerability and efficacy of the intravenous form of the drug.[119] In a double-blind, randomized, controlled trial in patients with treatment-refractory OCD, Fallon and coworkers found that nine of 21 patients treated with 14 days of clomipramine infusions and seven days of oral treatment were responders, compared with none of 18 in the placebo group. Improvement was maintained to the end of blind ratings at three weeks, and the regimen was well tolerated.[120]

Even experienced psychopharmacologists may be reluctant to administer some of the prospective treatments. A once-a-week opioid receptor agonist trial in OCD patients has shown some success and is under investigation.[77] Since potential adversities of these treatments are high, they should probably still be conducted only in specialized centers under scrutiny of researchers and with explicit informed consents until more evidence is gathered.

Non-Pharmacological Strategies:

Electroconvulsive therapy (ECT) has a role in cases of treatment-refractory OCD complicated by severe comorbid depression, but it is not believed to be consistently effective for primary treatment-refractory OCD. In one uncontrolled case series, the majority of patients with treatment-refractory OCD improved considerably for a year following such therapy.[121] Although the response was associated with improved depression ratings, the authors suggested an independent effect on obsessional symptoms.

Non-pharmacological experimental treatment strategies are under development and testing, including: **Deep Brain Stimulation (DBS), Vagus Nerve Stimulation (VNS), and Repetitive Transcranial Magnetic Stimulation (rTMS).**

Bilateral Deep Brain Stimulation (DBS) has been used successfully for essential tremor and Parkinson's disease (PD) since about 1995 and utilizes the Medtronic Activa Tremor Control System.[122] Significant adverse events from the DBS procedure have included equipment failure or lead wire breakage, intracranial hemorrhage, infection, seizures, and paresis. In 1999, a team of Swedish and Belgian physicians approached refractory OCD through DBS rather than bilateral capsulotomy.[123] The selected stimulation targets for the chronic stimulation were identical to those aimed for in a capsulotomy. In four patients with severe treatment-resistant OCD, quadripolar electrodes were stereotactically bilaterally implanted in the anterior limbs of the internal capsule. Beneficial effects were seen in three patients.

The vagus nerve (10th cranial nerve) is best known for its efferent function with parasympathetic inervation to organs such as the heart and gut. However, approximately 80% of vagal nerve fibers are afferent sensory fibers and relay information from the body to the brain.[124] These afferent fibers project via the nucleus tractus solitarii (NTS) to the locus ceruleus (LC) and parabracial nucleus (PB). The LC and PB project to all levels of the forebrain, including the hypothalamus, orbital frontal cortex, amygdala, and bed nucleus of the stria terminalis. In theory, direct stimulation of the vagus afferent fibers could affect sensory input to limbic, brain stem, and cortical areas known to be involved in mood and anxiety disorders. Vagus Nerve Stimulation (*VNS*) has had an excellent safety record in

seizure patients.[125] The most common adverse event related to implantation is mild pain at the incision site that typically resolves over the two weeks following surgery. There are currently seven patients with obsessive-compulsive disorder, two patients with PTSD, and one panic disorder patient implanted with the device. Acute and long-term data are not yet available on these patients.[126]

Barker and coworkers introduced *Transcranial Magnetic Stimulation* (rTMS) in 1985 as a non-invasive means of stimulating the cerebral cortex.[127] It involves placing an electromagnetic coil on the scalp and passing a rapidly alternating high-intensity current through the coil. This sets up a magnetic field, which passes through the cranium and induces local electrical changes on the surface of the cortex. Therapeutically, rTMS has received the most attention with treatment-resistant depression.[128,129] Greenberg and coworkers treated 12 patients with OCD and found that a single session of right prefrontal rTMS decreased compulsive urges for 8 hours, but there was no effect on obsessions.[130] However, Alonso and coworkers, who randomly assigned 18 patients with OCD to real or sham rTMS, did not find any difference between the treatment groups.[131]

With the failure to find effective therapies for OCD over the past three decades, *psychosurgery* has become an intervention of last resort.[132] It is important to balance the risks of nonintervention (social, physical, and psychological complications, including suicide) against those of surgery (frontal lobe dysfunction and psychological complications, including personality alteration, substance abuse, and suicide), which are not excessive with current techniques.[133] **Unfortunately, in the absence of a controlled comparison with "sham" surgery, efficacy remains unproven.** Follow-up studies from the 1960s and 1970s showing improvement in more than 80% of patients need to be viewed with caution, because many patients would not meet current criteria for treatment resistance or therapeutic response.[134] More-recent retrospective and prospective studies have reported response in 30% to 60% of patients. A "gamma knife" using cobalt 60 has been used in some centers to create surgical lesions without opening the skull, making a controlled comparison with sham surgery feasible.[135] The procedures favored across various centers include cingulotomy, subcaudate tractotomy, capsulotomy, and limbic leucotomy (cingulotomy plus subcaudate tractotomy).[136] No conclusive data exist on comparative efficacy or safety. Further research is needed to identify the best target sites. For these procedures, a "stereotactic" frame is used, and target sites are visualized with magnetic resonance imaging. Occasionally, surgeons will reoperate if clinically indicated. It is hypothesized that such lesions disrupt dysfunctional neural circuits by severing connections between the orbitomedial frontal lobes and limbic or thalamic structures. However, the observation that most patients take weeks or months to improve suggests that secondary effects such as nerve degeneration may be important. If the patient seems to be suitable, the next step is to contact the multidisciplinary review committee at an institution specializing in this form of neurosurgery for further details about their criteria for treatment and admission. Surgery should only be used as an absolutely last resort and performed in specialized centers.

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