

Pharmacotherapies in the Management of Obsessive–Compulsive Disorder

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Few medications are effective in treating obsessive–compulsive disorder (OCD). As monotherapy, only potent serotonin (5-HT) reuptake inhibitors (SRIs) consistently exert an intrinsic therapeutic action in OCD. Their use in OCD, however, differs from their use in depression. This paper first reviews the evidence supporting the key role of 5-HT as a pivotal neurotransmitter in the anti-OCD response. Then, we describe the practicalities of SRI use, followed by the steps that can be taken when these medications do not produce an adequate clinical response. We provide specifics for the treatment of children and adolescents with OCD. We include a brief description of the brain circuitry involved in OCD and the mechanisms of action of the pharmacologic agents reported to be effective in this disorder, as well as those that are useful in depression but not in OCD. We present this information to promote better understanding of the research endeavours needed to develop new pharmacotherapeutic approaches.

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Clinical Implications

- OCD is a chronic disorder amenable to pharmacotherapy using a single class of medications: the potent SRIs.
- With a good knowledge of the properties of these drugs, optimal response and patient safety and comfort can be achieved.
- It is possible to augment the anti-OCD response with various augmentation strategies.
- The response to various pharmacotherapies is generally partial, and their administration must be prolonged to avoid the resurgence of symptoms.

Limitations

- SRIs exert class side effects that are sometimes difficult to minimize.
- Few augmentation strategies are supported by double-blind studies.

Key Words: *serotonin, serotonin reuptake inhibitors, orbitofrontal cortex, basal ganglia, autoreceptors, atypical antipsychotics, glutamate, obsessive–compulsive disorder, pharmacotherapy*

The first reports of the potential for medications to exert an antiobsessional effect in patients without major depression were published about 35 years ago (1–4). The tricyclic antidepressant G-34586, or CMI, was used successfully in these first attempts. The serendipitous finding of its beneficial effect on obsessions in depression patients motivated its use in

that disorder. Several case series in the following decade seemed to confirm the usefulness of this medication in treating OCD, then denoted obsessive–compulsive neurosis. The first controlled trials demonstrating a therapeutic action of CMI in OCD were published in 1980 (5,6). These were followed by many positive studies (see 7 for a review).

At the time, there were still doubts whether CMI exerted its action in OCD because it was an antidepressant drug or because it was a true antiobsessional medication, despite the 1980 observation that it had been shown to be superior to the noradrenergic tricyclic nortriptyline and placebo in a randomized, albeit small, double-blind trial (6). The elegant controlled trials carried out in children by Rapoport's group, who used CMI and the noradrenergic tricyclic desipramine, established the specific action of CMI in OCD (8,9). In the first study, patients were randomized to either CMI or desipramine and then crossed over to the other drug, whereas in the second study, patients were randomized to CMI or desipramine for treatment prolongation after they responded to CMI. In both studies, desipramine was either ineffective or led to deterioration of prior CMI-induced improvement.

In the late 1980s and early 1990s, the nontricyclic SSRIs fluoxetine, fluvoxamine, paroxetine, and sertraline became available and were shown to be effective in treating OCD in multiple placebo-controlled studies (see 10–13). Several years later, citalopram was predictably shown to be an effective anti-OCD agent (14). Again, the demonstration that fluvoxamine, but not desipramine, was effective in OCD patients in a head-to-head, double-blind comparison helped consolidate the notion that the anti-OCD response of certain antidepressant medications is attributable to potent 5-HT reuptake inhibition (15). Further, the addition of desipramine in treating SSRI-resistant OCD patients was not an effective measure in a randomized, double-blind trial (16). The latter

observation is important because, although CMI is not a very potent NE reuptake inhibitor, its desmethylated metabolite, which is present in greater concentration than its parent compound in most patients taking CMI, is the most potent NE reuptake inhibitor available in human therapeutics (17).

SSRIs for the Treatment of OCD

These medications have all been shown to be effective in the treatment of OCD in placebo-controlled trials; they should be used as first-line agents. They can all be initiated at the same dosages as are recommended for the treatment of depression. It is unusual to see an exacerbation of anxiety in OCD patients when an SSRI is initiated at the usual recommended dosages (Table 1)—whereas it is common in patients with panic disorder. Nevertheless, it may be wise to tell patients to take one-half the dosage for the first few days and then increase it to the recommended dosages if there is no exacerbation of anxiety. In general, dosages higher than those used in depression are necessary to obtain an optimal anti-OCD effect. With fluoxetine, for example, titration is not pursued further in most depression patients who have not responded at all to 40 mg daily. By contrast, in a large controlled trial in OCD patients, the response to fluoxetine was best in the 60-mg daily treatment arm (18). Consequently, when an SSRI is used to treat OCD, the maximal recommended dosage, if tolerated, should be used before it is concluded that a patient is resistant to a particular drug. Finally, reports for some SSRIs indicate that, in some patients, additional benefits can be obtained from regimens beyond the maximal recommended dosages (19).

Another feature of the anti-OCD response to SSRIs is its longer delay, compared with the response to depression with the same medications. Indeed, trials of SSRIs in depression treatment generally last between 6 and 8 weeks, whereas in studying OCD response, they last between 10 and 12 weeks. Therefore, when treating OCD patients with an SSRI, a daily regimen of at least one-half the maximal recommended dosage should be achieved as soon as possible and then maintained for about 2 months before an attempt is made to reach the maximal recommended dosages, if the benefits are deemed suboptimal.

No useful predictive factors exist to orient the choice of SSRI, and with limited information currently available comparing SSRIs among each other (20), there does not seem to be any clear therapeutic advantage associated with any particular SSRI. Therefore, the choice should be based on their particular side effect profiles and on their potential for drug–drug interactions. For instance, fluoxetine may produce more agitation than the other SSRIs, which is why it is never prescribed at bedtime. Sertraline may produce more gastrointestinal problems, such as loose stools, whereas paroxetine may

Abbreviations used in this article

5-HT	serotonin
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CMI	clomipramine
CYP	cytochrome P450
ECG	electrocardiogram
GABHS	group A beta-hemolytic streptococcus
GLU	glutamate
mGLUR	metabotropic glutamate receptor
NE	norepinephrine
OCD	obsessive–compulsive disorder
OFC	orbitofrontal cortex
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections
SNRI	serotonin norepinephrine reuptake inhibitor
SRI	serotonin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

Table 1 Daily dosages of SRIs for the treatment of OCD

Medication	Starting dose (mg)	Initial targeted dose (mg)	Maximal dose (mg)
Citalopram	20	40	60
Escitalopram ^a	10	20	20
Fluoxetine	20	40	80
Fluvoxamine	50	200	300
Paroxetine	20	40	60
Sertraline	50	100	200
Clomipramine	25	150	250
Venlafaxine ^b	75	225	375

^aNot indicated for OCD, but its effectiveness is supported by one placebo-controlled trial

^bNot indicated for OCD, but a double-blind paroxetine-controlled study showed equal effectiveness

produce anticholinergic side effects, especially in susceptible individuals, such as elderly patients, because of its moderate affinity for muscarinic receptors (21). With regard to drug interactions, low dosages of paroxetine and fluoxetine and high dosages of sertraline, citalopram, and escitalopram will significantly inhibit *CYP2D6*, thereby raising the plasma levels of most antipsychotics, beta blockers, and certain antiarrhythmics (for example, flecainide and mexiletine; 22). Fluvoxamine inhibits the *CYP1A2* isoenzyme, thereby increasing the levels of olanzapine and clozapine; it also prolongs the half-life of caffeine from 6 to over 30 hours (23). All SRIs, with the exception of citalopram, escitalopram, and the SNRI venlafaxine, will enhance the anticoagulant effect of warfarin (24).

CMI for the Treatment of OCD

The tricyclic SRI, CMI is by far the medication with the longest record for the treatment of OCD. However, because of its cumbersome side effect profile and the toxicity associated with its tricyclic moiety, it should not be used as a first-line medication. Nevertheless, when deemed necessary, it should be initiated at 25 mg daily and increased progressively, according to tolerability and response, to about 150 mg daily. In some cases, however, only 75 mg may produce a clear therapeutic benefit (5). Nevertheless, it may be prudent to obtain a plasma level of CMI and its metabolite to ensure that the patient is not a slow *CYP2D6* metabolizer, in which case a regimen of 75 mg daily may already be in the upper-normal range and 150 mg daily may produce levels in the potentially toxic range. This would be expected in about 7% of patients of European ethnicity and in perhaps a higher percentage of African Americans (25). By contrast, a small percentage of patients may be ultrarapid metabolizers and have subtherapeutic levels even at maximal recommended dosages (200 mg daily or more; see 26).

It is clinical lore that OCD patients are generally more tolerant of medication side effects. That said, with CMI, the first side effects to occur may be nausea and anticholinergic discomforts (that is, dry mouth, constipation, urinary hesitancy, and abnormal vision). Although nausea usually dissipates in the first 2 weeks of treatment (possibly owing to the desensitization of 5-HT₃ receptors; see 27), the anticholinergic side effects may not abate over time and may even increase with ascending titration. Dizziness, headaches, tremors, fatigue, abnormal vision, dyspepsia, anorexia, and sexual dysfunction are among the most common side effects (28). Despite these drawbacks, CMI is still considered by many to be the gold standard for the treatment of OCD.

Direct Comparisons of SSRIs and the SRI CMI

Metaanalyses comparing the placebo-controlled trials of CMI and of the SSRIs came to the conclusion that CMI was a more effective medication (28,29). However, several factors could have influenced this conclusion, such as the period when the trials were carried out. Most of the CMI trials were carried out when SSRIs were not available. Therefore, most patients were not likely medication-resistant when CMI was tested; they possibly also tolerated more side effects, knowing that there were no pharmacologic alternatives. By contrast, when the SSRI trials were carried out, CMI was available in many countries, as were other SSRIs. Consequently, during the SSRI trials, there were possibly more treatment-resistant patients than in the CMI trials, although the former drugs were not commercially available. This may thus explain, at least in part, the larger effect size with CMI.

In support of the latter explanation, there are now 6 head-to-head, double-blind comparisons of various SSRIs and CMI, using sample sizes of at least 30 patients per

treatment arm, showing essentially no difference between the tricyclic and the SSRIs (30–35). As expected, however, tolerability was better for the SSRIs in most trials. In fact, the CMI–sertraline comparison yielded a small but significantly greater reduction of overall scores in the sertraline group at the end of the study. This apparent advantage was, however, attributable to a lower dropout rate in the sertraline group (34).

Long-Term Pharmacotherapy of OCD

There are hardly any data on the dosages of SRIs that should be used in treatment prolongation, compared with dosages used in the acute treatment phase. It would thus be prudent to maintain the regimen that produced the maximal improvement in the acute treatment. Given the chronic course of OCD, and its waxing and waning feature, there is a general consensus that the pharmacotherapy of OCD should definitely be prolonged. The most recent guidelines recommend a minimum treatment of 1 to 2 years, followed by a gradual taper to avoid discontinuation phenomena and monitor patients for a possible deterioration (36,37).

The Management of OCD Patients Following a First Failed Trial

After an SRI has failed to produce an adequate response, algorithms generally recommend using a second SRI and, only after that, to carry out a CMI trial. Drug combination generally appears further in such guidelines (36,37). Although guidelines and algorithms are useful, clinicians should always tailor therapeutic regimens to their patients and should not eliminate various options merely on the basis of guidelines. First, switching SRIs should be done effectively without wasting time in a cross-titration, considering that these drugs all inhibit the 5-HT transporter. For instance, when switching SRIs with similar half-lives, the first drug could be discontinued abruptly and the second one initiated at a dosage that is about in the middle of its therapeutic range. In such conditions, the elimination of the first drug takes place at a similar rate as the achievement of the steady-state level of the second medication and does not produce major fluctuations of 5-HT reuptake inhibition. By contrast, if fluoxetine were the first treatment, it could be stopped abruptly, but the second SSRI would have to be titrated slowly because the effect of fluoxetine and its metabolite on 5-HT reuptake remains for at least 4 weeks (22).

When a second SRI is chosen as a second step, efforts should be made to achieve greater reuptake inhibition. In some cases, this may be possible because the second SRI may be better tolerated than the first. From that perspective, it may be worthwhile considering using escitalopram (S-citalopram) as a second SRI. Indeed, several lines of evidence indicate that higher levels of synaptic 5-HT may be achieved when using

this enantiomer of racemic citalopram than when using another SRI (38,39). In the treatment of depression, controlled studies have shown that 10 mg daily of escitalopram is about equivalent to 40 mg of citalopram (40). This differential effectiveness appears to result from 2 factors. First, the R-enantiomer is inactive on 5-HT reuptake. Second, R-citalopram decreases the capacity of S-citalopram to inhibit 5-HT reuptake through its influence on a modulatory site that is located on the 5-HT transporter and that controls its function (41). It is worth mentioning that other SSRIs do not have pronounced activity at this other site, denoted an allosteric site, but that CMI, like escitalopram, promotes its own binding to the 5-HT transporter (41,42).

The implementation of CMI treatment has already been mentioned above, if this drug is considered as the next option. Given that CMI has a half-life in the same range as most of the other SRIs, no time should be wasted in the substitution, unless, again, a switch from fluoxetine is carried out. Even if fluoxetine were stopped abruptly, it would leave the patient at a slow metabolizer status for at least 2 to 3 weeks. Consequently, a rapid titration of CMI could produce toxic levels within the first month from a fluoxetine switch.

Like CMI, venlafaxine acts as dual 5-HT and NE reuptake inhibitor at high dosages (43). It also appears to be effective in treating OCD. Although there is no placebo-controlled study that establishes its efficacy, there is a large head-to-head comparison that uses high dosages of both agents, with high dosages of paroxetine showing identical outcome (44). It is thus expected that the dual reuptake inhibitor duloxetine will also be effective in OCD, provided high dosages are used (that is, 120 mg; see 45,46).

Strategies to Increase 5-HT Reuptake Inhibition in the Brain

As described above, potent 5-HT reuptake inhibition is the crucial effect for achieving an anti-OCD response. Several groups of investigators have attempted to achieve optimal degrees of 5-HT reuptake inhibition in the brain of OCD patients by injecting SRIs intravenously. This route of administration avoids the hepatic first-pass elimination occurring when such medications are given orally. Where CMI is injected intravenously, there will be more of this parent compound than of its desmethylated metabolite in the plasma for brain penetration. In a recent double-blind study, this approach appeared to produce a superior, although not confirmed, therapeutic response (47,48). A positive intravenous citalopram trial in OCD patients has also been reported (49).

This treatment strategy is, however, not readily available. Nevertheless, it is possible to readily obtain a ratio of high CMI to desmethylated metabolite by inhibiting this conversion process. Since the latter metabolic process mainly occurs

Table 2 Controlled studies that assessed the effectiveness of the addition of antipsychotics in OCD patients not responding to SRIs

Antipsychotic medication	Study	Antipsychotic dosage		Duration weeks	Outcome (<i>n</i> patients)
		mg daily	Mean (mg)		
Risperidone	McDougle and others (51)	1.0–6.0	2.7	6	Risperidone > placebo (<i>n</i> = 20, <i>n</i> = 16)
	Hollander and others (13)	0.5–3.0	2.1	8	Risperidone > placebo (<i>n</i> = 10, <i>n</i> = 6)
	Erzegovesi and others (53)	0.5	—	6	Risperidone > placebo (<i>n</i> = 20, <i>n</i> = 19)
	Li and others (54)	1.0	—	2	Risperidone > placebo (<i>n</i> = 12, <i>n</i> = 16)
Olanzapine	Shapira and others (58)	5.0–10.0	6.1	6	Olanzapine = placebo (<i>n</i> = 22, <i>n</i> = 22)
	Bystritsky and others (57)	5.0–10.0	11.2	6	Olanzapine > placebo (<i>n</i> = 13, <i>n</i> = 13)
Quetiapine	Denys and others (55)	300.0	—	8	Quetiapine > placebo (<i>n</i> = 20, <i>n</i> = 20)
	Fineberg and others (56)	50.0–400.0	215.0	16	Quetiapine = placebo ^a (<i>n</i> = 11, <i>n</i> = 11)
Haloperidol	McDougle and others (124)	2.0–10.0	6.2	4	Haloperidol > placebo ^b (<i>n</i> = 17, <i>n</i> = 17)
	Li and others (54)	2.0	—	2	Haloperidol > placebo ^c (<i>n</i> = 12, <i>n</i> = 16)

^a3 of 11 patients responded to quetiapine addition compared with 1 of 11 who responded to placebo.
^bOnly when tics were present
^c5 of 12 patients discontinued the medication because of side effects.
— = Medication was used at a fixed dosage

through the action of *CYP1A2*, the inhibition of this enzyme can achieve this end result. *CYP1A2* can be significantly inhibited with 50 to 100 mg daily of fluvoxamine. The plasma levels of CMI and its metabolite should, however, be monitored when attempting such a combination (50).

Addition of Atypical Antipsychotics To Potentiate the SRI Response in Resistant Patients

The only pharmacologic augmentation strategy for SRI-resistant patients that is supported by consistent results obtained in double-blind studies is the addition of some atypical antipsychotic medications (Table 2). The strongest results have been obtained with the addition of low dosages of risperidone (generally < 3 mg daily). All 4 double-blind studies using this medication reported positive results generally occurring within 2 to 6 weeks (51–54). The results of 2 controlled studies suggest that this strategy could possibly be extended to quetiapine addition: one positive study involved

40 patients; another, with 21 patients, had a somewhat, though not significantly, greater responder rate (55,56). Beyond these 2 agents, the results with other atypical antipsychotics are mixed. For instance, there is one positive and one negative double-blind study of olanzapine addition (57,58).

Pharmacotherapy of OCD in Children and Adolescents

Up to 80% of OCD cases begin during childhood or adolescence (59). Over the past 2 decades, several randomized, controlled clinical trials have been conducted in children (aged 6 years and older) and adolescents (aged up to 19 years) with OCD. These trials have demonstrated, as in adults, the selective and unique efficacy of SRIs in the short-term treatment (that is, 5 to 16 weeks) of the disorder. The earliest studies showed the superior efficacy of CMI (mean dosage 141 to 150 mg daily) over placebo (60,61) or desipramine (8). Interestingly, in one study, clinical improvement of the OCD symptoms during CMI administration was strongly correlated

with pretreatment platelet 5-HT concentrations and with the decrease of platelet 5-HT content during treatment (62). Later placebo-controlled studies have demonstrated the efficacy of fluoxetine (mean dosages 20 mg and 64 mg daily; 63,64), sertraline (mean dosage 150 to 167 mg daily; 65,66), and fluvoxamine (dosage range 50 to 200 mg daily; 67).

Consistent with the adult treatment literature, clinical trials in children and youth show the following:

- The anti-OCD action is independent of the presence of depressive symptoms at baseline.
- The anti-OCD action takes longer to appear than an antidepressant action.
- The therapeutic response is gradual over a few weeks or a few months.
- Response to active medication is most often incomplete, with a mean reduction from baseline on scales measuring intensity of OCD symptoms ranging from 19% to 44% across measures and across studies (68).

A metaanalysis of 12 randomized, controlled medication trials in children and adolescents with OCD (total $n = 1044$) concluded that serotonergic medications, including CMI, sertraline, fluvoxamine, fluoxetine, and paroxetine, were significantly superior to placebo in treating pediatric OCD, with consistent findings across studies but a modest overall effect size (0.46). CMI was statistically superior to the SSRIs in reducing OCD symptoms (69), possibly owing in part to temporal issues discussed above.

Worldwide, few SSRIs have been licensed for treatment of subjects aged younger than 18 years. In Canada, CMI is not recommended under the age of 10 years, and none of the SSRIs are approved for youth under the age of 18 years. However, from the literature cited above, the practice parameters for the assessment and treatment of children and adolescents with OCD (70,71) can recommend the SSRIs as safe, effective, and well tolerated in children and adolescents, with a side effect profile similar to that seen in adults. Systematic dose-response data are not available for children, but side effects generally appear dose-dependent. It is therefore recommended to start with a low dosage and increase it slowly up to the minimum dosage found effective in adult patients, although much higher dosages have been used in published studies (see above). For young children and those with a low body weight, dosage needs to be adjusted for weight. An adequate therapeutic trial of CMI generally consists of dosages up to 3 mg per kg daily for 3 months. CMI should not, however, be a first-line treatment in children and youth with OCD because of its pharmacokinetic properties and side effect profile. Risks of toxicity include seizures and ECG changes (therefore, ECG monitoring is recommended); rare cases of

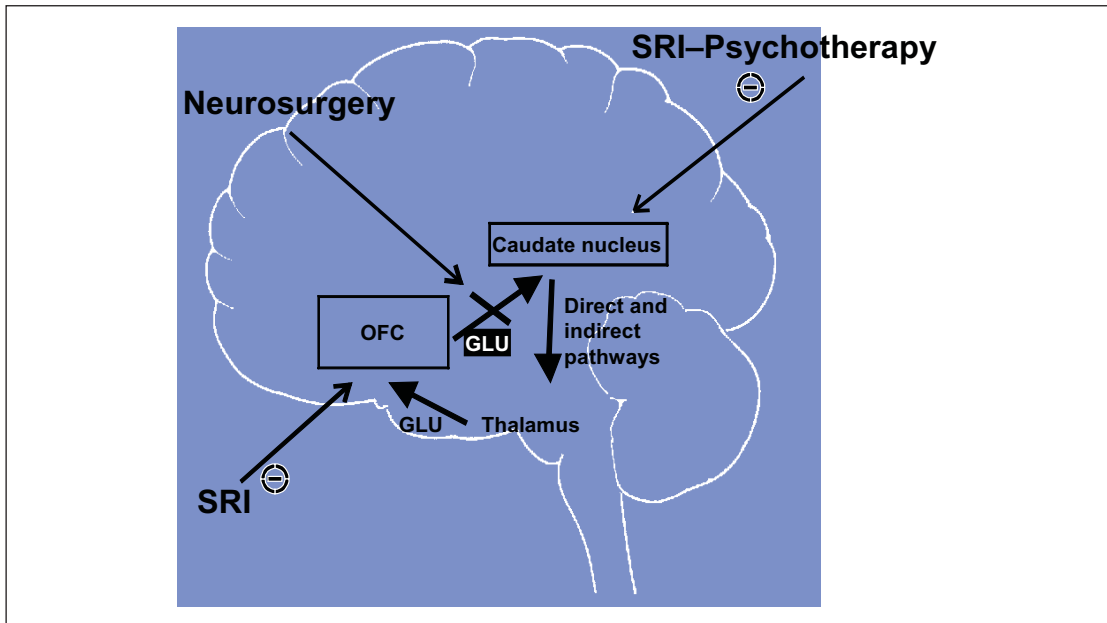
sudden death have been reported in children taking tricyclic antidepressants (72).

A recent and highly publicized concern has been a possible increased risk for suicidal thoughts, self-harm, and (or) harm to others in youth treated with SSRIs. In pooled analyses of the controlled studies conducted in youth with OCD and other anxiety disorders (73), behavioural side effects variously labelled as activation, akathisia, disinhibition, impulsivity, and hyperactivity have appeared, but no evidence has been found for a significant increase in the relative risk of suicidal thoughts or behaviours. The variability in placebo rates and the absence of actual cases of suicide preclude reliable conclusions, whereas the benefit–risk ratio for the treatment of OCD in youth remains positive. Nevertheless, rigorous clinical monitoring for suicidal ideation and other potential indicators for suicidal behaviour is advised in youth, as in older patients.

Tic disorders, including Tourette syndrome, are frequent comorbidities of childhood-onset OCD (74). In comorbid cases, SRIs alone may have few anti-OCD effects, and there are reports suggesting that fluvoxamine and fluoxetine may exacerbate, or even induce, tics in some patients (63). The adult literature and the few case reports of children and youth with OCD and comorbid tic disorder suggest that combined treatment with an SRI and a low dosage of risperidone or another antipsychotic medication may be useful (75). In OCD with comorbid attention-deficit hyperactivity disorder, an SSRI may be associated with a psychostimulant medication (76).

For the last decade, an autoimmune model of OCD that could apply to a subgroup of subjects whose disorder begins abruptly during childhood has attracted clinical and research interest. An association has been reported between acute-onset OCD and Sydenham's chorea, a childhood movement disorder associated with rheumatic fever, which is thought to result from an antineuronal antibody-mediated response to GABHS directed at portions of the basal ganglia (77). OCD or some of its symptoms are seen in 70% of Sydenham's chorea cases (78,79). Even in the absence of the neurologic symptoms of Sydenham's chorea, poststreptococcal cases of childhood-onset OCD, tics, and (or) other neuropsychiatric syndromes have been described under the acronym PANDAS. This novel group of patients was defined according to 5 diagnostic criteria: presence of OCD and (or) tic disorder; prepubertal onset; episodic course of symptom severity; abrupt onset or dramatic exacerbations of symptoms associated with GABHS infections, as evidenced by positive throat culture and (or) elevated anti-GABHS titers; and association with neurologic abnormalities (that is, motoric hyperactivity or adventitious movements, such as choreiform movements or tics; see 77). Therapeutically, the finding of a probable

Figure 1 Schematic representation of the major structures involved in the manifestation of OCD symptoms, the sites of action of various therapeutic interventions, and of some details on the neurochemical–anatomical features of these elements. SRIs decrease (–) the metabolic activity of the OFC and head of the caudate nucleus in OCD patients after prolonged treatment, as does effective psychotherapy in the latter structure. This is believed to result from enhanced 5-HT release occurring in the OFC. The neurosurgery intervention in this circuit consists of placing a lesion in the anterior limb of the internal capsules. GLU is the neurotransmitter used by monosynaptic pathways between the OFC and the caudate and between the thalamus and OFC. The links between the caudate and the thalamus are complex pathways within the basal ganglia; refer to (82) for more details.



autoimmune-caused OCD raises the clinical possibility that immunosuppressant treatments may be effective in treating or preventing some cases of OCD. This has been demonstrated in a double-blind, placebo-controlled study showing the efficacy of 2 immunomodulatory treatments in subjects with PANDAS (80). However, the first double-blind attempt to demonstrate the efficacy of penicillin prophylaxis in preventing tic or OCD symptom exacerbation was negative, possibly because an acceptable level of streptococcal prophylaxis was not achieved (81). It is unknown, as yet, what percentage of children with OCD may be part of the PANDAS subgroup, and for such cases, neither immunosuppressant nor antibiotic treatments are to be used outside the context of research board–approved protocols. Nevertheless, for prompt treatment, children with abrupt onset or exacerbation of OCD symptoms merit careful assessment of recent medical illnesses, including upper respiratory tract infections.

Brain Regions Involved in OCD

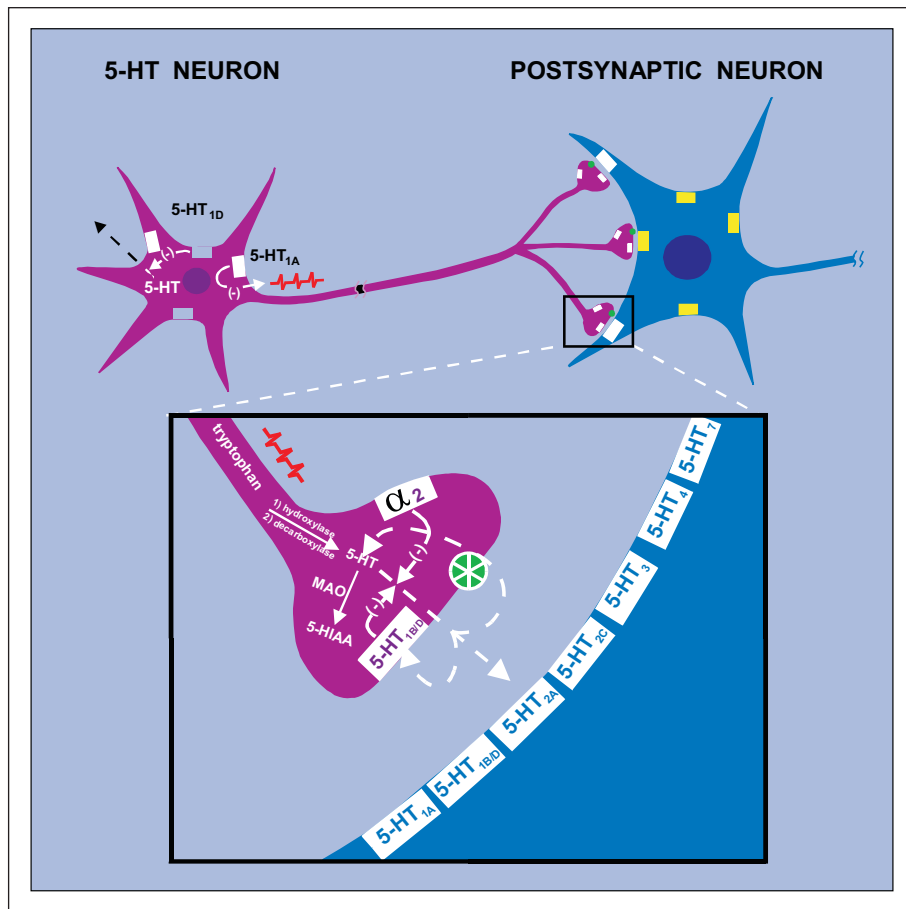
A good comprehension of the brain structures involved in OCD and (or) in the anti-OCD response is the first step to understanding the biological basis of the disorder and to eventually devising new therapeutic approaches. This is an unmet need because only one-half of OCD patients experience

significant benefits from SRIs. Further, when patients respond to treatment, the improvement is most often partial. Indeed, the OCD treatment–response criterion is generally an improvement of only 35% (and 25% in some cases) on the Yale–Brown Obsessive Compulsive Scale, whereas in depression a 50% amelioration is the norm.

Positron emission tomography studies have implicated specific brain areas in OCD, in particular, a neuronal loop involving the OFC, the head of the caudate nucleus, a direct and an indirect pathway through the basal ganglia, the thalamus, and back to OFC (82–85; Figure 1). There is an increased metabolic activity in these brain regions in OCD, and successful treatment, whether it is pharmacologic or behavioural, is associated with a normalization of their metabolic activity (85–87). Further, provocative stimuli that induce OCD symptoms increase regional cerebral blood flow in the OFC and the head of caudate nucleus (88). Electroencephalography studies have also revealed hyperactivity in the corticofrontal regions that is dampened on successful treatment (89,90).

In support of the abovementioned neuronal circuit's contribution to OCD, a lesion placed in the anterior limb of the internal capsule in severe and refractory patients may produce significant improvement (91,92). This intervention, which must be

Figure 2 Diagram of the 5-HT system illustrating the main elements controlling its function in the central nervous system. The rectangles depict the main membranal receptors controlling the function of 5-HT neurons and the mediation of the effect of 5-HT on postsynaptic neurons. Not all subtypes of postsynaptic 5-HT receptors are provided, only those for which an electrophysiological response has been documented. The Alpha2-adrenergic receptor depicted on the 5-HT terminal is sensitive to NE and is denoted a heteroreceptor; it can exert an inhibitory effect on 5-HT release that is as important as its neighboring 5-HT autoreceptor. The dotted lines show the movements of 5-HT into the synapse and within 5-HT neurons. The cogwheels on the terminals represent the 5-HT reuptake transporters, which are also present on the cell bodies of 5-HT neurons. The (-) signs represent an inhibitory influence on the release and (or) firing activity. MAO stands for monoamine oxidase and 5-HIAA for 5-hydroxyindole acetic acid, the main metabolite of 5-HT. Tryptophan is the amino acid precursor of 5-HT; tryptophan hydroxylase is located exclusively in 5-HT neurons and is not saturated under normal physiological conditions; the decarboxylase enzyme is contained in monoamine neurons at large. The (α) symbol represents alpha.



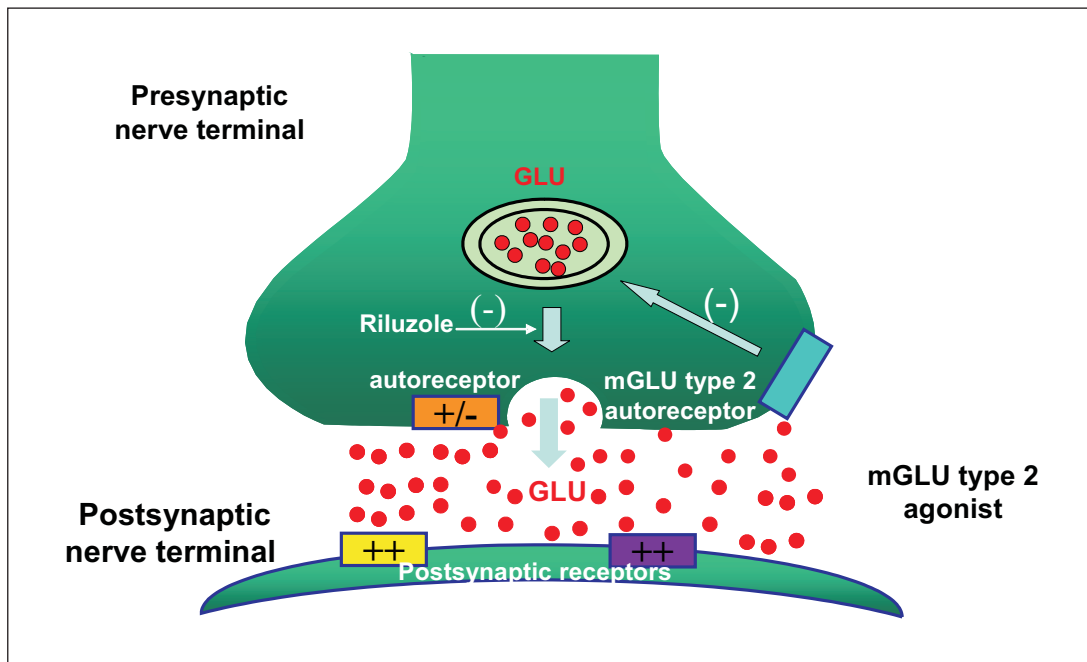
restricted to patients who have failed pharmacologic and psychotherapeutic interventions, interrupts the efferent pathway of the OFC to the caudate nucleus but does not cause cognitive impairment. The relative success of this approach has led to the implanting of deep brain-stimulating electrodes to, presumably, block neuronal conduction without producing an irreversible lesion (93,94). This procedure was first devised to treat severe cases of Parkinson's disease. Taken together, these results clearly indicate that the effects of useful medications should be studied in such brain structures and that drugs

for potential treatment should be able to alter the function of such structures before human therapeutics are considered.

Effects of Antidepressant Treatments on 5-HT Transmission

Several studies using various techniques have documented that all antidepressant treatments enhance 5-HT neurotransmission in the rat hippocampus (95). This net effect is, however, mediated via different pre- and postsynaptic mechanisms (see Figure 2). Because, among all antidepressant

Figure 3 Representation of a GLU synapse in the central nervous system, with GLU molecules represented by the small spheres in the synapse. In OCD, several lines of evidence indicate that there would be an enhanced activity of GLU neurons leading to increased synaptic concentrations of GLU. Riluzole is a medication that directly inhibits the release process of GLU. GLU terminals release its neurotransmitter under the influence of the electrical impulse flow, and it is modulated by presynaptic autoreceptors that can exert either a positive (+) or a negative (–) effect. The mGLU 2 receptors are denoted as such because they are coupled to a biochemical transducing mechanism, in contrast to several other types of receptors that are coupled to ion channels (called ionotropic receptors). The mGLU 2 receptors are located in most regions of the brain outside the synapse, where the concentration of GLU is the greatest. When activated, they inhibit GLU release only when it is increased above normal. Other important features of this receptor that make it a good therapeutic target are as follows: it does not desensitize when it is activated chronically, which suggests that there should be no tolerance of the beneficial effect of its activation; and abrupt cessation of its activation by an exogenous agonist does not lead to rebound effects.



treatments, only the SRIs are effective in treating OCD, a specific modification of the 5-HT system that they produce should account for their therapeutic benefit in this condition. Only the SRIs desensitize the terminal 5-HT autoreceptor. This receptor normally inhibits the amount of 5-HT that is released per impulse. In brain regions involved in OCD, its desensitization occurs after 2 months, whereas this desensitization requires only 2 weeks in structures involved in depression, such as the hippocampus and hypothalamus (96). This finding is consistent with the finding that, in OCD, the optimal therapeutic effect of the SRIs manifests itself after a longer delay than is observed in depression. In laboratory animals, such an adaptive change, which increases 5-HT release, was obtained with a high, but not a low, regimen of fluoxetine—which is consistent with the high dosages of SRIs usually required to treat OCD. Finally, electroconvulsive shocks, which remain the gold standard in the treatment of depression but are ineffective in treating OCD, did not alter

5-HT release in the guinea pig OFC after 12 sessions given thrice weekly (97).

In an attempt to obtain further 5-HT release in the presence of SRIs, tryptophan, the amino acid precursor of 5-HT, was added after the prior administration of the cell body 5-HT_{1A} antagonist pindolol (2.5 mg thrice daily) to prevent a decrease in firing activity of 5-HT neurons resulting from the increased conversion of tryptophan into 5-HT (98). Although the SRI–pindolol combination was found to be effective in a double-blind study (99), Blier and Bergeron did not observe an improvement of OCD symptoms with this combination, unless tryptophan was added at the rate of 1 to 3 g twice daily, titrated slowly over 4 weeks (98). These results thus make the terminal 5-HT autoreceptor a valuable target to develop either a new monotherapy or an adjuvant for SRIs in treating OCD. Although desensitized by SRIs, these autoreceptors remain somewhat responsive (96,97). Consequently, simultaneous blocking of 5-HT transporters together with the terminal

autoreceptor may result in a more rapid and (or) robust increase in 5-HT release than when an SRI alone is used. Such drugs have been synthesized but have yet to be thoroughly studied in patients. An additional line of indirect evidence supporting the important role of enhancing 5-HT release to obtain an anti-OCD effect stems from the lack of benefit of lithium addition in SRI-resistant OCD patients (100,101). It is well known that lithium, which is effective in treatment-resistant depression, increases 5-HT release in brain structures involved in depression, such as the hippocampus and hypothalamus, but that it is inactive on this parameter in areas implicated in OCD, such as the cerebral cortex and the striatum (102).

SSRI Effects on Postsynaptic 5-HT Receptors in Brain Regions Involved in OCD

It is important to emphasize that not only alterations of presynaptic neurotransmitter components can modulate synaptic transmission: postsynaptic 5-HT receptors also play a crucial role in controlling overall transmission. In the OFC, the responsiveness of 5-HT_{1A} receptors is attenuated after 3 and 8 weeks of sustained administration of an SSRI (103). It is therefore not surprising that the addition of the 5-HT_{1A} receptor agonist buspirone is not effective in SRI-resistant patients, as shown in 3 double-blind studies (104–106). Indeed, buspirone would be expected not to alter 5-HT_{1A} transmission at pre- and postsynaptic receptors because these receptors would have been desensitized by prior SRI administration (95,103).

In contrast to the desensitizing of 5-HT_{1A} receptors in the OFC after prolonged SRI administration, the inhibitory response to 5-HT itself and to 5-HT₂ receptor agonists remains unchanged (103). Consequently, 5-HT should thus exert its action in the OFC mainly via 5-HT₂ receptors. Further, these results, taken together with those showing that the response to nonselective 5-HT₂ agonists remains unaltered in mice lacking 5-HT_{2C} receptors, suggest that 5-HT_{2A} receptors principally mediate the effect of 5-HT in the OFC (107,108). These observations make 5-HT_{2A} agonists without hallucinogenic properties potential candidates to treat OCD. Such compounds are currently undergoing testing in our research unit.

Given such results, it may appear paradoxical that certain atypical antipsychotics, which are potent 5-HT_{2A} antagonists, are useful adjuncts in SRI-resistant patients. This may be explained by observations showing that 5-HT₂ receptors in the OFC are pharmacologically distinct from those in other regions of the cerebral cortex (109). A low dosage of risperidone blocks 5-HT₂ receptors in the medial prefrontal cortex but not in the OFC, whereas a high dosage is effective in the latter cortical subdivision (109). This observation is consistent with the potential of some atypical antipsychotics

to produce OCD symptoms *de novo* in schizophrenia patients or to exacerbate OCD when used at high dosages (110,111). Such high regimens could decrease 5-HT₂ transmission in the OFC, thereby producing or worsening OCD.

The beneficial action of atypical antipsychotics added to SRIs nevertheless remains to be explained. Risperidone and quetiapine appear effective and are the only 2 agents with alpha 2-adrenoceptor antagonistic potency equal to or higher than that for 5-HT_{2A} receptors (112). It can be hypothesized that these drugs remove the negative feedback action still exerted by the alpha 2-adrenoceptor on 5-HT terminals after the feedback action mediated by 5-HT autoreceptors has already been lifted by prior SRI treatment. In such a pharmacologic condition, 5-HT terminals would release more 5-HT because there would no longer be any direct negative feedback action (Figure 1). This possibility does not, however, appear consistent with recent reports of the beneficial action of mirtazapine in SSRI-resistant patients, despite this drug's having an affinity for alpha 2-adrenoceptors 10 times lower than its 5-HT_{2A} property (113–115). It remains to be determined, however, whether mirtazapine's apparent benefit is a true anti-OCD effect or a nonspecific anxiolytic action.

The Glutamate System as a Target for Anti-OCD Medications

Several lines of evidence indicate that a hyperglutamatergic activity is involved in OCD. First, a specific neurosurgical intervention, which lesions part of the anterior limb of the internal capsule, can produce significant improvement in treatment-refractory OCD patients (91,92). In that specific location, projections from the OFC course to the caudate nucleus. Because efferent axons from the OFC are from the pyramidal neurons, and because these neurons are glutamatergic neurons, it is likely that the neurochemical effect of capsulotomies is to interrupt increased glutamatergic transmission between the OFC and the caudate nucleus (Figure 3). Second, with magnetic resonance spectroscopy GLU determination techniques, OCD symptoms in youth were shown to be associated with abnormally increased levels of striatal GLU that normalized following SRI treatment (116,117). Therefore, a drug that could directly decrease GLU neurotransmission would in theory induce a rapid onset of action, in contrast to SRIs, which take several weeks to enhance inhibitory 5-HT transmission.

Such a net effect could be achieved by pre- or postsynaptic action in the GLU system (Figure 3). A first possibility would be to decrease GLU release. Recently, riluzole, a medication thought to act in amyotrophic lateral sclerosis by exerting this very effect, has been reported to be effective in treating SRI-resistant OCD patients (118). Another possibility would be to activate inhibitory autoreceptors on GLU terminals to

turn down excessive GLU release. These neurons are endowed with just such a subtype of autoreceptor, the mGLUR type 2, which exerts an inhibiting effect only when GLU release is increased (119). This hypothesis is supported by the observation that the signs of opiate withdrawal are blocked in rats by acute administration of the mGLUR type 2 agonist LY354740, although it produces no behavioural effects in normal rats (120). The therapeutic effect of such a drug should thus only depend on its reaching an adequate steady-state level in the brain. Such an agent has already been tested in humans, with positive results in an experimental model of anxiety (121). More potent and bioavailable compounds should allow the testing of this hypothesis in OCD.

Finally, partial antagonizing of postsynaptic GLU receptors in the OCD circuit may make it possible to obtain an anti-OCD effect (122, 123). The exact characterization of such receptors (the mGLUR type 5, AMPA, N-methyl-D-aspartate, or kainate receptors being the main candidates) remains to be carried out in the OCD circuit. However, effectively blocking these receptors could be a delicate and risky task because to decrease glutamatergic transmission to an extent similar to that achieved by capsulotomy, high dosages of an antagonist might be needed, which could lead to severe side effects.

In summary, there is currently only one class of anti-OCD agents that can be used in monotherapy, and their use in OCD differs somewhat from their use in mood disorders. Although several strategies can be used to potentiate SRIs in patients with an inadequate anti-OCD effect, only certain atypical antipsychotics have been shown to be effective augmenting agents in controlled studies. Numerous other pharmacologic compounds can be added to SRIs, but their efficacy has yet to be established. Results from some positive case series appear to support the potential for the development of new pharmacologic strategies. Such a research effort is crucial because, if symptom improvement is the rule in OCD, complete and durable remission remains the exception.

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Résumé : Les pharmacothérapies dans le traitement du trouble obsessionnel-compulsif

Peu de médicaments sont efficaces pour traiter le trouble obsessionnel-compulsif (TOC). Comme monothérapie, seuls les puissants inhibiteurs du recaptage de la sérotonine (IRS; 5-hydroxytryptamine ou 5-HT) exercent de façon constante une action thérapeutique intrinsèque sur le TOC. Cependant, leur utilisation pour le TOC diffère de celle pour la dépression. Cet article présente d'abord les données probantes qui appuient le rôle clé des 5-HT comme neurotransmetteurs essentiels de la réponse anti-TOC. Puis, nous décrivons les détails concrets de l'utilisation des IRS, suivis des mesures à prendre quand ces médicaments ne produisent pas une réponse clinique adéquate. Nous présentons les particularités du traitement pour les enfants et les adolescents souffrant du TOC. Nous incluons une brève description des circuits du cerveau impliqués dans le TOC et des mécanismes de l'action des agents pharmacologiques reconnus efficaces pour ce trouble, ainsi que de ceux qui sont utiles pour la dépression, mais pas pour le TOC. Nous présentons cette information pour promouvoir une meilleure compréhension de la nécessité d'entreprendre des recherches pour élaborer de nouvelles approches pharmacothérapeutiques.