Bahrain Medical Bulletin, Vol. 34, No. 2, June 2012

Antipsychotic Treatment in OCD

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Due to the phenotypical heterogeneity of Obsessive-Compulsive Disorder (OCD) and its subtypes, and due to the high rate of co-morbid psychopathology, it remains a challenge to treat OCD using medication effectively, behavioral therapy and cognitive therapy.Selective serotonin reuptake inhibitors (SSRIs) arefirst-line pharmacotherapy treatments OCD, but up to 50% of patients do not respond to initialtreatment of OCD.Therefore, treatment options for non-respondersinclude augmentation of antidepressantswith antipsychotics and other medications.

Bahrain Med Bull 2012; 34(2):

After Post Traumatic Stress Disorder, OCD is the highest anxiety disorder, which has initiated more research over the last three decades[1]. Meta-analysis has proven that treatment is effective using either pharmacotherapy with SRIs alone or in combination with cognitive behavioral therapy. Unfortunately, 38% of patients are treatment refractory (not experiencing clinically significant benefits) and only 30% of patients were asymptomatic after treatment[1,2].

It is well established that there is a need to report the effectiveness of interventions in routine clinical practice as well as the efficacy studies in patients with comorbidities. In addition, we need to study the outcome using varying methods aside from simple significance tests of pre and post symptoms severity comparison. Furthermore, analysis of group means, investigators must assess the responses of each individual patient for reliable and significant change. There are a few published studies concerning the outcome of Cognitive Behavioral Therapy(CBT) in cases of severe OCD[1].

Theaim of this review is to define treatment-resistant OCD and to evaluate the effectiveness of treatment of severe OCD.

The Etiology of OCD

There have been numerous postulations about the cause of OCD. These have evolved from demon possession to melancholia, the result of overt scrupulousness and eventually it was perceived as “neurasthenia”. Some believed that it stemmed from faulty beliefswoven into a pattern of thought and behavior. While others claimed that dissociative pathology was the cause[2].

Freud was finally instrumental in describing OCD as the result of psychological defenses, which protects against unconscious anxiety[3]. More scientific theories regarding its origin

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and careful clinical picture has been described and improved upon in the current DSM-IV. The psychological models of OCD have now been challenged by the relatively recent evidence for a biological basis as progress in genetic research revealed a significant role of hereditary[3,4].

Neuroimaging revealed neural pathway disturbances in thebasal ganglia, subcortical areas of the brain and the orbito-frontal cortex. Both dopamine and serotonin disturbances supportthe pathophysiology of OCD[5]. Medical conditions, suchas teratoma, endocrine disturbance, neoplasm andtoxin exposures might produce symptoms of OCD; example of this is pediatric autoimmune neuropsychiatricdisorder (PANDAS) and streptococcal infection in veryyoung children.OCD is extremely complex in term of its causative factors.

Thereappears to be a combination of genetic and socio-psychological factors.Identifying the elements of the disorder is often confounded by thepresence of comorbidities, external environmental influences and thepresence of significant dissociation. The role of diatheses (constitutionalfactors that predispose the body to certain illnesses or conditions)in OCD is inescapable. Some scientists proposed that theetiology of OCD could be viewed best from the framework of a stressdiathesismodel. This integrative model encompasses biological andsocio-psychological factors. They alsothought that OCD should be thought of as a spectrum of manifestationsthat extends from the most biologically determined to the mostpsychologically determined[6].

Treatment-resistant OCD

OCD is a chronic psychiatric disease characterized by recurrent and persistent thoughts (obsessions) and/or repetitive compulsive behavior (compulsion). These must cause the individual anxiety, are time-consuming and cause a significant socio-occupational dysfunction. Even with pharmacological and behavioral treatments, the outcome is not satisfactory for 40-60% of OCD patients[7].

There have been several attempts to define and stage treatment-resistant OCD, see table 1. An estimated 5% of OCD cases have an episodic course, 40-60% of OCD patients' fails to improve sufficiently with first line management and considered refractory[4].

It is only reasonable to include recovery and remission in the staging terminology. Guy defined Adequacy, Resistance and Refractoriness of treatment[7]. A trial is considered 'Adequate' if the patient has been given first-line pharmacotherapy in the form of at least three SSRIs at the maximum recommended dosage for minimum of 12 weeks and the treatment should have included the use of clomipramine and/or behavioral therapy with at least 20 hours of exposure and response prevention (ERP).

Failure to respond to the above trial is considered treatment resistance. Resistance is considered failure to respond to one SSRI,i.e. less than 25% reduction on the Yale Brown Obsessive-Compulsive Scale (Y-BOCS)[7,8]. It may be argued that it is not absolute since most treatment resistant cases are actually cases of relative resistance to drugs. It might be considered accurate to divide resistance to drug resistance and treatment resistance. Drug Resistance is considered when the patient shows less than 25% reduction on the Y-BOCS after treatment with at least two SSRIs. Treatment Resistance is considered when the patient fails to show response to the above plus 20 hours of compliant ERP[7]. Refractoryis failure to respond to two SSRIs.

Table 1: Stages of Response in Obsessive-CompulsiveDisorder

Definition	
Stage I Recovery/not at all ill	Less than 8 on Yale-BrownObsessive Compulsive Scale (Y-BOCS)
Stage II Remission	Less than 16 on Y-BOCS
Stage III Full response	35% or greater reductionof Y-BOCS and CGI 1 or 2
Stage IV Partial response	Greater than 25% but lessthan 35% Y-BOCSreduction
Stage V Non-response	Less than 25% Y-BOCSreduction, CGI 4
Stage VI Relapse	Symptoms return (CGI 6 or25% increase in Y-BOCS from remission score) after3+ months
Stage VII Refractory	No change or worsening,with all available therapies

Subtypes of OCD

It is now believed that OCD is a heterogenous condition with several subtypes. We can subdivide OCD depending on age of onset (e.g. earlier age with familial form), the presence of tic disorders and comorbid psychiatric disorder, each with a potential implication to treatment. For example, a patient with OCD and comorbid tics is usually has an early onset with a specific range of OCD symptoms and responds very poorly to SRIs[7].

In addition, it is believed that "psychotic OCD" exist, which in the DSM-4 called "OCD without insight", usuallyare poor responders[2].Further study of the response to treatment and illness trajectory and outcome may help us further subdivide OCD in the future[8].

Epidemiology of OCD

OCD is estimated to be 10% of patients in psychiatry clinics. It is the fourth most common psychiatric disorder after phobias, substance related disorders and major depressive disorder. The female to male ratio is equal but the presentation is earlier in males (mean age in males is 19 compared to females 22 years). The first onset of symptoms is before the age 25 for two-thirds of patients, and only 15% of patients present after age 35. The onset could be in childhood or adolescence and the earliest reported case was 2 years of age[9].

It is more frequent in single persons, perhaps reflecting the difficulty of maintaining a relationship. It is more often in whites compared to blacks, although this variation could be due to access to healthcare. The prevalence of Obsessive-compulsive personality disorder(OCPD)among patients with OCD is similar to its prevalence among other psychiatric disorders[2,4].

Patients with OCD are commonly afflicted by other mental disorders; for instance, the lifetime prevalence for a major depressive episode in these patients is around 67%. Other common comorbid psychiatric diagnoses include alcohol-use disorders, social phobia, specific phobia, panic disorder and eating disorders. The comorbidity of schizophrenia and with tic disorders raises interesting pathophysiological and therapeutic implications. The rate of tic disorders approaches 40% in juvenile OCD and there is an increase in the prevalence of Tourette's syndrome among the relatives of OCD patients[2].

Treatment of OCD

A combination of a potent serotonergic agent and CBT is considered themost effective treatment. The behavioral component consists of EPR[10]. Exposure is helpful in reducing obsessions and response prevention is helpful in reducing compulsive behaviors. Potent 5-HT reuptake inhibitors (SSRIs; clomipramine) are considered the first-line medications for the treatment of OCD. SSRIs are preferred over clomipramine solely because of their lower propensity to cause side effects[11].

Medications treatment of OCD should take 8-12 weeks or longer and it requires higher dosage of drugs compared to other neurotic disorders, i.e. generalized anxiety disorder and depression.

Medication should be continued for a minimum of 1 year and possibly indefinitely. With adequate treatment, the average reduction in obsessions and compulsions is about 50%, only 5% to 10% of individuals eventually becoming symptom free. If the first-line treatments of SSRIs and clomipramine failed, alternative treatments are required,see table 2[12].

Table 2: Pharmacologic Treatment of OCD

OCD		Examples	Recommended Dose for Adult (mg/day)
Standard Treatment	SSRI	Citalopram	20-60
		Escitalopram	10-20
		Fluoxetine	20-60
		Fluvoxamine	100-300
		Paroxetine	40-60
		Sertraline	50-200
Alternative Treatment	TCA	Clomipramine	75-300
	SNRI	Venlafaxine	150-225
	NaSSA	Mirtazapine	30-60
	MAOI	Phenelzine	45-90

The Yale-Brown Obsessive-Compulsive Scale is commonly used to evaluate patients with OCD and reduction in symptoms of 25-35% is considered the threshold for response. Unfortunately, 40-50% of OCD patients fail to meet these criteria. Before we can say that the patient is treatment resistant, we must first make sure that the diagnosis is correct,the patient is compliant to treatment, the dosage is therapeutic and the trial period is adequate. Other drugs may interfere with efficacy, e.g. metabolic enhancers or inhibitors[13]. Psychosocial factors and personality may affect outcome. Depression and substance abuse may complicate OCD.

If the patient fails to show response after 8-12 weeks, the medication should be changed. However, if there is partial response, the patient may show improvement after an additional 4-6 weeks of therapy[7].

Other strategies evaluated in controlled studies are augmentation of SSRI or clomipramine with atypical (or typical) antipsychotic, seetable 3.There is a positive effect of antipsychotic

drug augmentation as evaluated by meta-analysis[7]. Clomipramine and clonazepam given intravenously has been effective in controlled trials. Other trials evaluated are demonstrated in Table 3.

Table 3:Treatment Options of Patients withOCD Who Are Unresponsive to Standard Treatment

RandomizedControlled Studies
Antipsychotic augmentation to SSRI or clomipramine
Intravenous clomipramine
Clonazepam
Open Studies
Addition of clomipramine to an SSRI
Buspirone
Topiramate
V-acetylcysteine
Addition of gabapentin to an SSRI
Addition of l-tryptophan to clomipramine or to SSRIplus pindolol
Glutamate antagonist Riluzole
NMDA receptor antagonist memantine
Combination of citalopram and reboxetine
Aripiprazole
Psilocybin
Gonadotropin-releasing hormone analogue triptorelin
Nicotine chewing gum

Treatment Strategies for Resistant OCD Patients (Table 4)

A practical approach should include the following[7]:

1. Primary physicians should perform early screening to detect juvenile-onset or adolescent OCD.
2. The consideration of different diagnosis if required.
3. The use of antipsychotics to augment the trial if needed.
4. Identifying comorbidities.
5. Considering the psychosocial issues.
6. Making use of non-drug treatments (CBT, group/individual therapy).

Table 4: Other Augmenting Agents

Drugs	**Action/ Dose**	**Side Effects**
Clonazepam	Up-regulation of 5-HT1 and 5-HT2 receptor in the frontal cortex	Depression, irritability and intoxication
Buspirone	Partial 5-HT1A receptor agonist at dosage of 10-90 mg/day	Irritability and forgetfulness
Lithium	Enhancement of 5-HT transmission	Neurotoxicity
Fenfluramine	Increases 5-HT neurotransmisson across the synaptic cleft	Not approved for use by FDA, considering its cardiac side effects and risk of pulmonary hypertension
Trazodone	50-100 mg/day	Sedation, priapism
Inositol	Only a few case trials reported	
Phenelzine	OCD with associated panic	Hypertensive crisis (or cheese reaction)

Venlafaxine	(1 Open trial and 2 reported case studies have found venlafaxine to have anti-obsessional activity in treatment-resistant OCD	Hypertension (at higher doses)
Sumatriptan	100 mg/day (5-HT1D agonist)	
Clonidine	Trials only in comorbid tics or Tourette's syndrome at dose of0.2-0.5 mg/day in three divided doses	Postural hypotension, dry mouth, irritability and headache

Antipsychotic Treatment in OCD (Table 5)

The use of typical neuroleptic to treat anxiety disorders was common in the 1970-1980s, but later, it was abandoned. In recent years, atypical antipsychotics were used to augmentnon-responsive OCD patients[14].

Pharmacokinetic Effects

The augmentation with quetiapine and SRIs are not fully explained by pharmacokinetic interaction[8].

Pharmacodynamic Effects

The pharmacodynamics mechanism of action of atypical antipsychotics in OCD has been studied by examining a group and specific agent and their relationship to known receptor binding agents[8].

Table 5: Antipsychotic Treatment in OCD

OCD		Examples	Recommended Dose for Adult (mg/day)	Mechanism of Action
Antipsychotic agents for patients with partial response to antidepressants	Typical	Haloperidol	> = 3	D_2 blockage, H_1, muscarinic, α_1, α_2-adrenergic & serotonergic receptors
		Pimozide	2-12	D_2 blockage, H_1, muscarinic, α_1, α_2-adrenergic & serotonergic receptors
	Atypical	Risperidone	0.5-2	Antagonist for the 5-HT_{2A}, 5-HT, D_2, D_3, D_4, H_1, α_1, & α_2 receptors, & weak affinities for the 5-HTT_{2C}, 5-HT_6, & muscarinic receptors
		Olanzapine	5-15	Antagonists for the 5-HT_{2A}, 5-HT_{2C}, D_1, D_2, D_4, α_1, H_1, & M_1& M_2 muscarinic receptors
		Quetiapine	150-750	Antagonists for the 5-HT_{2A}, 5-HT_7, D_2, 5-HT_{1A}, & α_1

Mechanism of Action of Antipsychotic in OCD

1) Atypical Antipsychotic

The serotonin dopamine antagonists (SDAs) are also known as second-generation or atypical antipsychotic drugs. These drugs include risperidone (Risperdal), olanzapine (Zyprexa),

quetiapine (Seroquel), clozapine (Clozaril) and ziprasidone (Geodon). They are called SDAs because they have a higher ratio of serotonin type 2 (5-HT2) to D2 dopamine receptor blockades than the typical or conventional, dopamine receptor antagonists (DRAs) that previously were the mainstay of treatment[16,17].

All SDAs share the following characteristics: 1) low D2 receptor blocking effects compared with DRAs, which have high D2 receptor blockades; 2) reduced risk of extrapyramidal side effects compared with older agents, reduced risk that probably extends to theoccurrence of tardive dyskinesia as well; 3) proved efficacy as treatments for schizophrenia; and 4) proved efficacy as treatments for acute mania[2,3,5].

Patients who do not respond to SSRIs may have additional abnormalities in dopamine function and thus require augmentation with dopamine blockers. It is believed to work via antagonism of both D2 and 5HS receptors. In psychosis, augmentation with risperidone 2-6mg/day and olanzapine 5-20 mg/day are effective in low doses[18].

A trial of 4 weeks at the maximum dose is sufficient. At present, there is no justification for the use of Clozapine due to its relative toxicity. There was a single placebo-controlled trial using Quetiapine but it was limited by small sample size. The indications were comorbid tic, delusional disorder, obsessions bordering on delusions. Quetiapine was limited by side effects including sedation, weight gain and EPS[7].

2) Typical Antipsychotic

The typical antipsychotic drugs vary in their in vitro and in vivo affinities for receptors such as the dopamine D_1, histamine H_1, muscarinic, α_1,α_2-adrenergic and serotonergic receptors, which modulate their effects on arousal, extrapyramidal, cognitive, cardiovascular, gastrointestinal and genitourinary function. Pimozide is a relatively potent antimuscarinic agent. Most of the low-potency antipsychotic agents are potent α_1 and H_1 antagonists[2,3,5].

In OCD patients with comorbid tic disorder or Trichotillomania, typical antipsychotics, i.e. haloperidol and pimozide, were used to augment OCD treatmentsuccessfully. This was not the case in treatment-resistant OCD. Neuroleptic agents like typical antipsychotics are used to augment SSRIs but carry the risk of inducing EPS and tardive dyskinesia[7].

CONCLUSION

In most cases, a combination of drug treatment and CBT may control symptoms and improve the quality of life for OCD patients. Studies have confirmed that augmentation of SSRIs with antipsychotics helps in SRI-refractory cases. Further controlled studies are needed to examine the efficacy of various atypical agents that may be used in augmentation, their dosage, duration of treatment and predictors of response. Additional research is needed to study the complexities and the exact mechanism of action and to divide OCD into subtypes according to psychobiology and phenomenology.

It is important to identify the patients with refractory OCD and switch them to a more effective pharmacological and/or psychological agent. Those patients who did not

respond after switching them to another pharmacological or psychological treatment may still have a chance to improve using intensive specialist treatment regimen.

Author contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes

Potential conflicts of interest: No

Competing interest: None **Sponsorship**: None

Submission date: 3 February 2012**Acceptance date**: 30 April 2012

Ethical approval: Faculty Research Committee, University of Dammam.

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