N-ACETYL CYSTEINE AUGMENTATION THERAPY FOR OBSESSIVE-COMPULSIVE DISORDER

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DISCLOSURES

- No conflicts of interest to disclose.

OBJECTIVES

- Discuss obsessive-compulsive disorder (OCD)
- Summarize current N-acetylcysteine uses and theories
- Review available literature regarding n-acetylcysteine as augmentation therapy in OCD patients
- Compare and contrast n-acetylcysteine treatment recommendations in varying OCD patient populations

PATIENT CASE

- HS is a 19 year old female seen for increasing worry and complaints of repetitive counting and handwashing.
- She states something bad will happen if she doesn’t continue to count until 12 at least two times and wash her hands twice with at least 4 pumps of soap each.
- She also states that she has found herself checking the door locks and electrical appliances at least twice before leaving her apartment.
- HS reports these thoughts have increased significantly since starting college.
- She denies any suicidal ideation or substance dependence. She is currently not pregnant nor breastfeeding.
- HS is eventually diagnosed with moderate obsessive-compulsive disorder.

BACKGROUND

OBSESSIVE-COMPULSIVE DISORDER
OBSESSIVE-COMPULSIVE DISORDER (OCD)

- Common, chronic and long-lasting disorder
- Uncontrollable, recurring thought (obsessions) and behaviors (compulsions)
- Urges to repeat over and over
- Estimated 1.2% of U.S. adults had OCD in the past year
- Lifetime prevalence among U.S. adults: 2.3%
- Mean age of onset for OCD
- More common in males for early-onset OCD; slight female predominance for adults

ETIOLOGY

OCD Etiology

Biological
- Serotonin hypothesis
- Brain imaging
- Genetics
- Neuroimmunology

Psychological
- Psychodynamic
- Personality
- Behavior

Social
- Accommodation
- Adaptive mechanisms

PATHOPHYSIOLOGY

- Abnormalities in serotonin transmission
- Abnormalities in dopaminergic transmission
- Evidence suggests abnormalities of the glutamatergic system may play a role in pathophysiology of OCD

DSM-V DIAGNOSTIC CRITERIA

A. Presence of obsessions, compulsions, or both:
- Obsessions and persistent thoughts, urges, or impulses that are experienced at some time during the disturbance as intrusive and unwanted, and that in most individuals cause marked anxiety or distress
- The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action

B. The obsessions or compulsions are time-consuming or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance or another medical condition

D. The disturbance is not better explained by the symptoms of another mental disorder

STAGES OF RESPONSE

- Obsessive-compulsive disorder stages of response
- Recovery
- Remission
- Full response
- Partial response
- Nonresponse
- Relapse
- Refractory

- Obsessive-compulsive disorder stages of response
- Recovery
- Remission
- Full response: 10-20% YBOCS ± 15
- Partial response: between 20% and 30% YBOCS reduction
- Nonresponse: 20% YBOCS reduction, CB1 or 2
- Relapse: Symptoms return > 6 months after 8 months of treatment at adequate dosage
- Refractory: No change or worsening of symptoms with all available treatments
TREATMENT GUIDELINES

<table>
<thead>
<tr>
<th>Level of Intervention</th>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed therapy</td>
<td>Exposure therapy and CBT (2014)</td>
<td>CBT</td>
<td>CBT or clomipramine with CBT</td>
</tr>
<tr>
<td>SSRI</td>
<td>SSRIs: escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline</td>
<td>Clomipramine, citalopram, clomipramine, mirtazapine, venlafaxine XR</td>
<td>SSRI or clomipramine with CBT</td>
</tr>
<tr>
<td>SNRI</td>
<td>SNRI: venlafaxine XR</td>
<td>Adjunctive: aripiprazole, risperidone</td>
<td>Duloxetine, phenelzine, tramadol, tranylcypromine</td>
</tr>
<tr>
<td>Adjunctive</td>
<td>Adjunctive: aripiprazole, risperidone</td>
<td>Adjunctive: memantine, quetiapine, topiramate</td>
<td>Adjunctive: celecoxib, granisetron, ondansetron, haloperidol, IV ketamine, mirtazapine, NAC, olanzapine, pindolol, pregabalin, riluzole, ziprasidone, citalopram</td>
</tr>
</tbody>
</table>

Other treatment: Augmentation with antipsychotics or pindolol

Clonazepam, clonidine, and desipramine NOT recommended

Citalopram, mirtazapine, memantine, clomipramine + SSRI, clomipramine + lithium, SSRI + buspirone or topiramate or pindolol

KNOWLEDGE CHECK

Which of the following would be the best initial treatment for HS?

- A) SSRI
- B) CBT
- C) 2 SSRIs + CBT
- D) Neurosurgery
- E) A and B

N-ACETYLCYSTEINE (NAC)

Common names: acetylcysteine, NAC
Pharmacologic category: antidote, mucolytic agent
Converted to cysteine (substrate for glutamate/cystine antiporter) → increases extracellular glutamate
Increased glutamate reduces synaptic release of glutamate
Many indications
Administration - oral, intravenous, inhalation

USES

FDA Indications
- Acetaminophen overdose
- Administration of anesthetics for procedure
- Analgesia due to nerve damage
- Bronchopulmonary disease, status
- Complication of surgical procedure - Respiratory complication
- Cystic fibrosis, Pulmonary complications,Adjunct
- Diagnostic procedure or lower respiratory tract
- Disease of respiratory system, chronic
- Tracheostomy care

Non-FDA Uses
- Acute respiratory distress syndrome
- Hepatic failure, acute, Non-Acetaminophen Induced
- Radiographic contrast agent nephropathy, Prophylaxis

GLUTAMATE RELATION

Excitatory neurotransmitter in the brain
Involved in a wide range of functions
Glutamate concentration significantly higher in cerebrospinal fluid of OCD patients compared to healthy controls
Higher glutamate concentration related to excitotoxicity and oxidative stress among patients with OCD, correlated with symptom severity
NAC and cysteine modulate extra and intracellular glutamate exchange through a known antiporter, ultimately resulting in reduction of glutamate synaptic release
PHARMACOKINETICS

Absorption
- Time, inhalation, nebulizer: 1-2 hours
- Time, oral effervescent tablet: 2 hours

Distribution
- Protein binding: 66% to 87%
- Vd: 0.47 L/kg

Metabolism
- Hepatic: rapid and extensive deacetylation to cysteine or oxidation to diacetylcysteine
- Cysteine, N,N-diacetylcysteine, N-acetylcysteine: activity unknown

Excretion
- Renal: 0.21 L/hour/kg; about 30% totally body clearance
- Renal clearance: 13% to 38%
- Dialyzable: yes (HD 51%, continuous venovenous hemofiltration 14.06%)
- Total body clearance: 0.11 L/hr/kg; 6.5 L/hr (healthy adults); 4.5 L/hr or decreased 30% (hepatic impairment)
- Elimination Half-Life
  - Adults: 5.6 hours, IV; 18.1 hours, oral effervescent tablet
  - Newborns: 11 hours

ADVERSE EFFECTS

Common
- Dermatologic: Pruritus (1% to 3%), Rash (4% to 5%), Urticaria
- Gastrointestinal: Diarrhea, Nausea (2% to 7%), Vomiting (9% to 12%)

Serious
- Cardiovascular: Decreased cardiac function, Electrocardiogram abnormal, Hypervolemia
- Immunologic: Anaphylactoid reaction (0.1% to 0.2%), Hypersensitivity reaction (Adult, 8% to 18%; pediatric, 10%)
- Neurologic: Status epilepticus
- Respiratory: Bronchospasm, Respiratory distress

PATIENT CASE

HS was started on sertraline about 4 months ago and is now taking 200mg/day. She states her symptoms have begun to creep back up and feels very uncomfortable in her daily tasks.
- She has continually refused CBT and states she wants to use another medication.
- Her doctor suggests starting fluoxetine, but HS is hesitant to use a medication from the same class as sertraline.

Could NAC be an option to try at this point?

SCALES

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)
- 10-item, clinician-administered scale for OCD
- Designed to rate symptom severity not diagnosis
- Sum of first 5 items is a severity index for obsessions, and sum of last 5 items an index for compulsions
- Total Scores
  - Mild OCD = 8-15
  - Moderate OCD = 16-22
  - Severe OCD = 23-40
  - Extreme OCD = 41-60

Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)
Pediatric Quality of Life Inventory (PedsQL™ 4.0 Generic Score Scales)
Clinical Global Impression-Severity (CGI-S) Scale
Beck Depression Inventory (BDI)
Beck Anxiety Inventory (BAI)
Brown Assessment of Beliefs Scale (BABS)
TRIALS

N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial

TRIAL SETTING, DESIGN AND PATIENTS

- Randomized, double-blind, placebo-controlled trial
- 10-week, conducted from July 2013 to March 2015
- Outpatient clinics of Roozbeh and Imam Hospitals

Inclusion
- DSM-IV-TR criteria for moderate-to-severe OCD
- Scored ≥21 in Y-BOCS
- Between 18 and 60 years old
- Did not receive any psychotropic medications for 6 weeks prior to study

Exclusion
- Suicidal ideation
- Substance dependence
- Intelligence quotient <70
- Comorbid medical illness, as well as severe cardio, renal, hepatic or other serious medical illnesses
- History of psychosurgery
- Significant head trauma
- Pregnancy
- Breastfeeding

TREATMENT GROUPS

- 82 patients screened
- 46 randomized
- 23 fluvoxamine + placebo
- 23 fluvoxamine + NAC

OUTCOMES

- Y-BOCS at baseline, fourth, eighth, and ten weeks

Primary Outcome Measure | Secondary Outcome Measures
--- | ---
Difference in Y-BOCS total score from baseline to end of trial between the two groups | Change difference in Y-BOCS obsession subscale score from baseline to week 10 between the two groups
Change difference in the Y-BOCS compulsion subscale score from baseline to week 10 between the two groups | Partial response rates (defined as <25% reduction in the Y-BOCS score)
Complete response rates (≥35% reduction in Y-BOCS score) | Remission rates (score ≤16) of the two groups at the end of the trial

RESULTS

- Y-BOCS total score, obsession subscale score, and compulsion subscale score

<table>
<thead>
<tr>
<th>Y-BOCS (mean ± SD)</th>
<th>NAC group</th>
<th>Placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>27.04 ± 4.39</td>
<td>25.81 ± 3.83</td>
<td>0.32</td>
</tr>
<tr>
<td>Obsession subscale</td>
<td>13.59 ± 2.42</td>
<td>12.95 ± 1.91</td>
<td>0.33</td>
</tr>
<tr>
<td>Compulsion subscale</td>
<td>13.63 ± 2.23</td>
<td>12.95 ± 2.19</td>
<td>0.33</td>
</tr>
</tbody>
</table>


RESULTS

- YBOCS total score (primary)
  - Repeated-measures ANOVA showed a significant effect for time treatment interaction (p=0.012).
  - Remission − borderline significant (p=0.062).
  - Partial or complete response − insignificant (p=0.54).

- YBOCS obsession
  - Repeated-measures ANOVA showed a significant effect for time (p=0.011).

- YBOCS compulsion
  - Repeated-measures ANOVA − the effect for time x treatment interaction; not significant in the compulsion subscale (p=0.33).


AUTHORS’ CONCLUSIONS

NAC might be effective for treatment of moderate to severe OCD with acceptable tolerability and minimal adverse effects.

NAC tolerability as well as its good safety profile and lack of significant interaction with standard OCD medications further highlight its potential benefits as add-on therapy for refractory OCD.


PRESENTER’S CRITIQUE

Small sample size

May be useful in moderate to severe OCD

May not be useful in management of more severe forms of OCD

Effects of higher NAC doses on OCD not determined.

Efficacy of N-Acetylcysteine Augmentation on Obsessive Compulsive Disorder: A Multicenter Randomized Double Blind Placebo Controlled Clinical Trial


TRIAL SETTING, DESIGN AND PATIENTS

- Multicenter, randomized, double-blind parallel group trial
- 10 weeks, conducted from March 2011 to April 2012
- Outpatient clinics of Shiraz University of Medical Sciences and Roozbeh Psychiatric Hospital

Inclusion

- K-SADS and DSM-IV TR criteria for OCD and OCD symptoms chronicity for at least 1 year
- Between 10 and 21 years old

Exclusion

- Substance use
- Serious co-morbid medical conditions
- Clinical increased renal regulation
- Primary diagnosis of psychosis
- Suicide attempt
- Recent Tourette disorder or ADHD needing treatment
- Breathing disorder
- Lack of adequate and reliable contraception
- Previous unsuccessful psychotherapy
- Unable to understand or follow instructions

TREATMENT GROUPS

50 patients invited
11 with no consent
5 aged >21 years
34 allocated to groups
19 NAC group
15 placebo group

NAC group (citalopram + NAC, 1 fluoxetine + NAC, 2 fluvoxamine or sertraline + NAC)
Placebo group (citalopram + placebo, 1 sertraline + placebo)

OUTCOMES

Y-BOCS at baseline, fourth, eighth, and ten weeks

Primary Outcome Measure
Difference in Y-BOCS total score change from baseline to end of trial between the two groups

Secondary Outcome Measures
Mean change of Y-BOCS score of resistance/control to obsessions from baseline to end of trial between the two groups
Mean change of Y-BOCS score of resistance/control to compulsions from baseline to end of trial between the two groups
Changes of PedsQLTM4.0 Generic Core Scales from baseline to 10 weeks between the two groups
Number and rate of adverse effects between the two groups

RESULTS

Age, Gender Ratio, and Y-BOCS Mean in Both Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>NAC group (n=18)</th>
<th>Placebo group (n=11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) years of age</td>
<td>16.5(2.9)</td>
<td>15.9(3.7)</td>
<td>p=0.6</td>
</tr>
<tr>
<td>Number (%) of female</td>
<td>7(38.9)</td>
<td>7(63.8)</td>
<td>p=0.1</td>
</tr>
<tr>
<td>Y-BOCS score at baseline</td>
<td>21.0(8.2)</td>
<td>22.5(8.4)</td>
<td>p=0.6</td>
</tr>
<tr>
<td>Y-BOCS score at week 4</td>
<td>16.6(6.9)</td>
<td>19(6.1)</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Y-BOCS score at week 8</td>
<td>13(7.0)</td>
<td>18(7.9)</td>
<td>p=0.06</td>
</tr>
<tr>
<td>Y-BOCS score at week 10</td>
<td>11.3(5.7)</td>
<td>19(7.7)</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

RESULTS (CONTINUED)

Within Group Changes of Y-BOCS Score in the Two Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between baseline and week 4</td>
<td>NAC</td>
<td>4.3(4.8)</td>
<td>2.6(5.7)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Difference between baseline and week 8</td>
<td>NAC</td>
<td>8.0(5.9)</td>
<td>4.0(7.7)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Difference between baseline and week 10</td>
<td>NAC</td>
<td>9.6(6.0)</td>
<td>2.6(7.7)</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>

RESULTS (CONTINUED)

Other results

<table>
<thead>
<tr>
<th>Group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference between week 4 and week 8</td>
<td>NAC</td>
</tr>
<tr>
<td>Mean difference at week 10</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mean score change of resistance/control to obsessions</td>
<td>NAC</td>
</tr>
<tr>
<td>Mean score change of resistance/control to compulsions</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

RESULTS (CONTINUED)

Within Groups Changes of Quality of Life Score

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>10 weeks</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical function</td>
<td>NAC</td>
<td>11.5(3.5)</td>
<td>6.6(3.2)</td>
</tr>
<tr>
<td>Emotional function</td>
<td>Placebo</td>
<td>10.4(3.5)</td>
<td>9.9(18.1)</td>
</tr>
<tr>
<td>Social function</td>
<td>NAC</td>
<td>7.4(3.6)</td>
<td>5.4(4.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.7(5.4)</td>
<td>5.4(4.0)</td>
<td>0.049</td>
</tr>
</tbody>
</table>
RESULTS (CONTINUED)

- The rate of none of the adverse effects was statistically different between the groups.
- Most common adverse effects:

<table>
<thead>
<tr>
<th>NAC group</th>
<th>Placebo group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (n=11)</td>
<td>Fatigue (n=4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Sweating (n=10)</td>
<td>Sweating (n=3)</td>
<td>0.96</td>
</tr>
<tr>
<td>Dizziness (n=6)</td>
<td>Dizziness (n=2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Blurred vision (n=4)</td>
<td>Blurred vision (n=2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Insomnia (n=5)</td>
<td>Insomnia (n=2)</td>
<td>0.60</td>
</tr>
<tr>
<td>Tremor (n=5)</td>
<td>Tremor (n=1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Anorexia (n=3)</td>
<td>Anorexia (n=4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Headache (n=5)</td>
<td>Headache (n=4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Dry mouth (n=4)</td>
<td>Dry mouth (n=4)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

AUTHORS’ CONCLUSIONS

NAC is effective in treating medication-resistant OCD symptoms in children and adolescents.

NAC may add to the effect of citalopram in improving some aspects of resistance/resolution and insight in patients with OCD.

NAC plus citalopram improved the domains of quality of life of patients with OCD.

NAC is well tolerated; many of adverse effects were rare.

NAC as an adjuvant agent to SSRIs improves resistance/control over compulsion symptoms in children and adolescents with OCD.

PRESENTER’S CRITIQUE

Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder


TRIAL SETTING, DESIGN AND PATIENTS

- Randomized, double-blind, placebo-controlled trial.
- 16-week data collected from May 2012 to October 2014.
- Outpatient clinics of the OCD Spectrum Disorders Program, Institute of Psychiatry, University of São Paulo Medical School.

TREATMENT GROUPS

- 145 assessed for eligibility
- 89 excluded
- 56 allocated
- 22 NAC group
- 34 placebo group
OUTCOMES

Primary Outcome Measure
• Y-BOCS score: evaluate the variables’ group, time, and interaction effects for Y-BOCS scores at all time points

Secondary Outcome Measures
• Mean reduction of baseline BDI, BAI, BABS, and Y-BOCS scores

RESULTS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>P Value</th>
<th>New Main Effect</th>
<th>Group Effect</th>
<th>Times Group Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y-BOCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>12.4(2.2)</td>
<td>10.9(1.5)</td>
<td>12.7(2.4)</td>
<td>18.5(5.4)</td>
<td>2.062</td>
<td>.095</td>
<td>.012</td>
</tr>
<tr>
<td>Complications</td>
<td>15.1(4.1)</td>
<td>15.4(3.6)</td>
<td>14.9(4.5)</td>
<td>14.1(4.8)</td>
<td>2.063</td>
<td>.096</td>
<td>.012</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

No benefit of NAC as an SRI augmentation agent for primary OCD symptoms, as indexed by the Y-BOCS.

AUTHORS’ CONCLUSIONS

No benefit of NAC as an SRI augmentation agent for primary OCD symptoms, as indexed by the Y-BOCS.

Adding NAC to stable SRI treatment is superior to placebo in reducing severity of anxiety symptoms.

PRESENTER’S CRITIQUE

Small sample size

Patient Case

After much nervousness, HS decided to try fluoxetine after all. She has been on 60mg/day for the past 3 months, but claims it is not working.

She states her schoolwork and grades have suffered and has been experiencing increasing anxiety about failing and worry about not performing her rituals correctly.

Her Y-BOCS score was 22.

Based on the literature, would NAC be an appropriate option to try?
CONCLUSIONS

- NAC might be effective for treatment of moderate-to-severe OCD and reduction in anxiety symptoms, though further studies are needed to establish a firm claim.
- NAC appears to be well-tolerated as compared to current OCD treatment agents.
- CBT or SSRI should remain first-line treatment recommendations for OCD.
- Clomipramine should remain as a second- or third-line option for SSRI treatment failure in OCD.
- Augmentation with other established agents should be considered in patients with partial response to OCD treatment.

REFERENCES


ACKNOWLEDGEMENTS

- Preceptor: Jacqueline Meaney, PharmD, BCPP
- Resident Program Director: Kendra Phillips, PharmD, BCPP
- Clinical Pharmacy Specialist in VATVCBHCS

QUESTIONS!
Appendices

Appendix A. Treatment Guidelines
Appendix B. Treatment Algorithm for Treatment-Resistant OCD: Levels of Nonresponse
Appendix C. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)
### Appendix A. Treatment Guidelines

#### TREATMENT GUIDELINES

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>Exposure therapy and CBT SSRIs</td>
<td>SSRI: escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline SNRI: venlafaxine XR Adjunctive: aripiprazole, risperidone</td>
<td>Exposure therapy and CBT SSRI: escitalopram, fluoxetine, fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td>Second-line</td>
<td><strong>Clomipramine</strong></td>
<td>Citalopram, <strong>clomipramine</strong>, mirtazapine, venlafaxine XR Adjunctive: memantine, quetiapine, topiramate</td>
<td><strong>Clomipramine</strong></td>
</tr>
<tr>
<td>Third-line</td>
<td><strong>SSRI or clomipramine with CBT</strong></td>
<td>Duloxetine, phenelzine, tramadol, tranylcypromine Adjunctive: celecoxib, granisetron, ondansetron, haloperidol, IV ketamine, mirtazapine, NAC, olanzapine, pindolol, pregabaline, risperidone, ziprasidone, citalopram</td>
<td>SSRI + haloperidol, quetiapine, olanzapine, or risperidone</td>
</tr>
<tr>
<td>Other treatment</td>
<td>Augmentation with antipsychotics or pindolol</td>
<td>Clonazepam, clonidine, and desipramine NOT recommended</td>
<td>Citalopram, mirtazapine, memantine, clomipramine+SSRI, clomipramine+thioridone, SSRI+buspirone or topiramate or pindolol</td>
</tr>
</tbody>
</table>
Figure. Treatment algorithm for treatment-resistant OCD: levels of nonresponse

1. SSRI or CBT
2. SSRI + CBT
3. 2 SSRIs tried + CBT
4. At least 3 SSRIs tried + CBT
5. At least 3 SSRIs (including CMI) tried + CBT
6. At least 3 SSRIs + CMI augmentation + CBT
7. At least 3 SSRIs + CMI augmentation + CBT + psychoeducation + another class of medication
8. At least 3 SSRIs + intravenous CMI + CBT + psychoeducation
9. At least 3 SSRIs + intravenous CMI + CBT + psychoeducation + other classes of antidepressants
10. All above treatments + neurosurgery

OCD, obsessive-compulsive disorder; CBT, cognitive-behavioral therapy; CMI, clomipramine hydrochloride.

* Benzodiazepine, mood stabilizer, neuroleptic, psychostimulant.

* Nonselective serotonin reuptake inhibitor, monoamine oxidase inhibitor.

Appendix C. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

## Obsessive-Compulsive Test - Yale Brown OCD Scale YBOCS

<table>
<thead>
<tr>
<th>Obsessions</th>
<th>(0)</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much time do you spend on obsessive thoughts?</td>
<td>None</td>
<td>0-1 hrs/day</td>
<td>1-3 hrs/day</td>
<td>3-8 hrs/day</td>
<td>More than 8 hrs/day</td>
</tr>
<tr>
<td>2. How much do your obsessive thoughts interfere with your personal, social, or work life?</td>
<td>None</td>
<td>Mild</td>
<td>Definite but manageable</td>
<td>Substantial interference</td>
<td>Severe</td>
</tr>
<tr>
<td>3. How much do your obsessive thoughts distress you?</td>
<td>None</td>
<td>Little</td>
<td>Moderate but manageable</td>
<td>Severe</td>
<td>Nearly constant, Disabling</td>
</tr>
<tr>
<td>4. How hard do you try to resist your obsessions?</td>
<td>Always try</td>
<td>Try much of the time</td>
<td>Try some of the time</td>
<td>Rarely try, Often yield</td>
<td>Never try, Completely yield</td>
</tr>
<tr>
<td>5. How much control do you have over your obsessive thoughts?</td>
<td>Complete control</td>
<td>Much control</td>
<td>Some control</td>
<td>Little control</td>
<td>No control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compulsions</th>
<th>(0)</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. How much time do you spend performing compulsive behaviors?</td>
<td>None</td>
<td>0-1 hrs/day</td>
<td>1-3 hrs/day</td>
<td>3-8 hrs/day</td>
<td>More than 8 hrs/day</td>
</tr>
<tr>
<td>7. How much do your compulsive behaviors interfere with your personal, social, or work life?</td>
<td>None</td>
<td>Mild</td>
<td>Definite but manageable</td>
<td>Substantial interference</td>
<td>Severe</td>
</tr>
<tr>
<td>8. How anxious would you feel if you were prevented from performing your compulsive behaviors?</td>
<td>None</td>
<td>Little</td>
<td>Moderate but manageable</td>
<td>Severe</td>
<td>Nearly constant, Disabling</td>
</tr>
<tr>
<td>9. How hard do you try to resist your compulsive behaviors?</td>
<td>Always try</td>
<td>Try much of the time</td>
<td>Try some of the time</td>
<td>Rarely try, Often yield</td>
<td>Never try, Completely yield</td>
</tr>
<tr>
<td>10. How much control do you have over your compulsive behaviors?</td>
<td>Complete control</td>
<td>Much control</td>
<td>Some control</td>
<td>Little control</td>
<td>No control</td>
</tr>
</tbody>
</table>

### Your Score:
If you have both obsessions and compulsions, and your total score is:
- 8-15 = Mild OCD
- 16-23 = Moderate OCD
- 24-31 = Severe OCD
- 32-40 = Extreme OCD

No single test is completely accurate. You should always consult your physician when making decisions about your health.

### References