Evidence-Based Pharmacotherapy for OCD: An Update.

Naomi A Fineberg

Highly Specialised Service for Obsessive Compulsive and Related Disorders, Hertfordshire Partnership NHS University Foundation Trust and University of Hertfordshire, Queen Elizabeth II Hospital, Welwyn Garden City, Hertfordshire AL7 4HQ
Declaration of interests

I have received sponsorship for:

• Consultancy work, from Servier, Lundbeck, Glaxo-Smith Kline, Astra-Zeneca and Bristol-Myers Squibb.
• Lectures, from Astra-Zeneca, Jazz Pharmaceuticals
• Educational support, from Janssen, Lundbeck, Bristol-Myers Squibb, Wyeth, Servier, Jazz.
Aims of lecture

• What are the first-line treatments?
• Does pharmacotherapy improved health-related quality of life?
• How do we evaluate clinical response and relapse?
• How long should treatment continue?
• Can we predict treatment outcomes?
• What is the management of treatment-refractory OCD?
Diagnostic category, Obsessive-Compulsive and Movement-Related Disorders.
Contains diagnoses that were listed in DSM-IV under Anxiety Disorders, Somatoform Disorders and Impulse-Control Disorders Not Elsewhere Classified

300.3 Obsessive-Compulsive Disorder a Specify if: Tic-related
300.7 Body Dysmorphic Disorder a Specify if: With muscle dysmorphia
300.3 Hoarding Disorder a Specify if: With excessive acquisition
312.39 Hair-Pulling Disorder (Trichotillomania)
698.4 Skin Picking (Excoriation) Disorder
--- Substance-Induced Obsessive-Compulsive or Related Disorders
294.8 Obsessive-Compulsive or Related Disorder Associated with a Known General Medical Condition
300.3 Other Specified Obsessive-Compulsive or Related Disorders
300.3 Unspecified Obsessive-Compulsive or Related Disorders

a Specify if: With good or fair insight, With poor insight, With absent insight/delusional beliefs
Anxiety Disorders Guidelines covering OCD

- International Consensus Group on Depression and Anxiety (2000, 2003)
- World Council on Anxiety Disorders (2003)
- National Institute for Clinical Excellence (UK) (2006; Evidence Update 2013)
- British Association for Psychopharmacology (2005, 2013 in press)
- American Psychiatric Association (2007)
Hierarchy of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from a single randomised controlled trial or a meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from at least one other well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports or opinions and/or clinical experiences of respected authorities</td>
</tr>
<tr>
<td>P</td>
<td>Pharmacological evidence from pre-clinical studies</td>
</tr>
</tbody>
</table>

Adapted from Eccles M & Mason J (2001), Mann T (1996)
Exclusion criteria in standard RCTs

- suicide risk and a history of self harm
- severe depression
- chronic depression
- recurrent depression
- treatment-resistant depression
- inpatients
- medical illnesses
- concurrent medication
- other psychiatric co-morbidity
- alcohol / substance misuse
- major social difficulties / chaotic lifestyles
- not taking contraception

Zimmerman et al, 2002
National Institute for Clinical Excellence (NICE) OCD Guideline

Key Priorities

• Awareness of OCD as major lifespan disorder
• Access to specialist services according to stepped care model
• Availability of behavioural cognitive therapies (incl ERP) and pharmacotherapies (SSRIs & CMI)
• **Behaviour therapy or pharmacotherapy 1st line for adults**
• Behaviour therapy 1st line; pharmacotherapy 2nd line for children
• **Combined behaviour therapy & pharmacotherapy in more severe cases**

www.nice.org.uk (Feb 2006)
Who is responsible for care?

**STEP 1** Individuals, public organisations, NHS

**STEP 2** GPs, practice nurses, school health advisors

**STEP 3** GPs and primary care team, primary care mental health worker, family support team.

**STEP 4** Local multidisciplinary care (GP or psychiatrist).

**STEP 5** Multidisciplinary teams with specific expertise in management of OCD (regional).

**STEP 6** Inpatient care or intensive treatment programmes (national).
First - Line Treatments in OCD

A. Behaviour therapy; exposure and response prevention (>16h; in vivo)

B. Pharmacotherapy; serotonin reuptake inhibitors (clomipramine or SSRI); higher doses; extended duration-minimum 12 weeks; adjunctive DA antagonists

C. Combination of A+B

BUT
Up to 40% fail to respond
Relapse is common
Better treatments are needed

The pharmacological specificity of OCD

<table>
<thead>
<tr>
<th>Effective</th>
<th>Ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Potent SRIs eg:</td>
<td>• Tricyclics (apart from clomipramine)</td>
</tr>
<tr>
<td>- clomipramine</td>
<td>• Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>- fluvoxamine</td>
<td>• Lithium</td>
</tr>
<tr>
<td>- fluoxetine</td>
<td>• Benzodiazepines</td>
</tr>
<tr>
<td>- sertraline</td>
<td>• Buspirone</td>
</tr>
<tr>
<td>- paroxetine</td>
<td>• Electroconvulsive therapy</td>
</tr>
<tr>
<td>- citalopram</td>
<td></td>
</tr>
<tr>
<td>- escitalopram</td>
<td></td>
</tr>
</tbody>
</table>

**Effective in combination with SRIs (unlicensed for OCD):**

- 1st generation antipsychotics eg haloperidol
- 2nd generation antipsychotics eg risperidone, quetiapine, olanzapine, aripiprazole
Are all antidepressants also anti-obsessive?
Randomised, double-blind, parallel-group study

Mean Y-BOCS score

Weeks

0 1 2 3 4 5 6 7 8

Goodman et al (1990) Arch Gen Psychiatry 47:577-585
Definitions of response for OCD

Depends on dose and duration of treatment

Response = 35% improvement in YBOCS (Full) OR 25% (Partial) AND/OR CGI-I Score 1 or 2


Standardised definitions of meaningful OCD response could be improved using combined clinical databases, as for other anxiety disorders (Bandelow et al. 2006).

By correlating post-baseline Y-BOCS improvements with CGI-I scores, changes smaller than those representing ‘much improved’ could be considered as ‘partial response’.

Fineberg NA et al J Psychopharmacol 2007
Which SRI?
Controlled studies comparing SSRIs with clomipramine (CMI)

<table>
<thead>
<tr>
<th>DRUG STUDY</th>
<th>n</th>
<th>DESIGN</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoxetine (FLX)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piggott et al (1990)</td>
<td>11</td>
<td>CMI (50-250mg) vs FLX (20-80mg)</td>
<td>CMI=FLX</td>
</tr>
<tr>
<td>Lopez-Ibor et al (1996)</td>
<td>30 vs 24</td>
<td>CMI 150mg vs FLX 40mg</td>
<td>FLX &gt; CMI</td>
</tr>
<tr>
<td><strong>Fluvoxamine (FLV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smeraldi et al (1992)</td>
<td>10</td>
<td>CMI 200mg vs FLV 200mg</td>
<td>CMI=FLV</td>
</tr>
<tr>
<td>Freeman et al (1994)</td>
<td>30 vs 34</td>
<td>CMI (150-250mg) vs FLV (150-250mg)</td>
<td>FLV = CMI</td>
</tr>
<tr>
<td>Koran et al (1996)</td>
<td>42 vs 37</td>
<td>CMI (100-250mg) vs FLV (100-250mg)</td>
<td>FLV &gt; CMI (on severe effects)</td>
</tr>
<tr>
<td>Milanfranchi et al (1997)</td>
<td>13 vs 13</td>
<td>CMI (50-300mg) vs FLV (50-300mg)</td>
<td>FLV = CMI</td>
</tr>
<tr>
<td>Rouillon (1998)</td>
<td>105 vs 112</td>
<td>CMI (150-300mg) vs FLV (150-300mg)</td>
<td>FLV &gt; CMI</td>
</tr>
<tr>
<td><strong>Paroxetine (PAR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zohar and Judge (1996)</td>
<td>99 vs 201 vs 99</td>
<td>CMI (50-250mg) vs. PAR (20-60mg) vs PLACEBO</td>
<td>CMI&gt;PLACEBO PAR&gt;PLACEBO</td>
</tr>
<tr>
<td><strong>Sertraline (SER)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisserbe et al (1997)</td>
<td>82 vs 86</td>
<td>CMI (50-200mg) vs. SER (50-200mg)</td>
<td>SER=SERI</td>
</tr>
<tr>
<td><strong>Citalopram (CIT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pidrman &amp; Tuma (1998)</td>
<td>24</td>
<td>CIT vs. CMI</td>
<td>CIT=CIT</td>
</tr>
</tbody>
</table>
For **paroxetin**e, n= 399 cases / 387 controls, mean change 2.73kg (0.78 – 4.68) based on 5 trials (2 major depression, 3 anxiety disorders)

Which dose?
Fixed – dose escitalopram study: primary analysis

**p<0.01; difference versus placebo**

Adjusted mean change from baseline
Y-BOCS total score

-14 -12 -10 -8 -6 -4 -2 0

0 4 8 12 16 20 24

Treatment week (LOCF)

Placebo n=113
Escitalopram 10 mg n = 114
Escitalopram 20 mg n=114
Paroxetine 40 mg n=116

* p<0.05, **p<0.01; difference versus placebo
## Placebo-controlled comparator studies of fixed-doses of SSRI

<table>
<thead>
<tr>
<th>DRUG STUDIES</th>
<th>FIXED DOSE</th>
<th>n</th>
<th>DURATION</th>
<th>Positive dose-response relationship?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20/40/60mg</td>
<td>214</td>
<td>8weeks</td>
<td>YES</td>
</tr>
<tr>
<td>Montgomery et al (1993)</td>
<td>20/40/60mg</td>
<td>214</td>
<td>13 weeks</td>
<td>NO</td>
</tr>
<tr>
<td>Tollefson et al (1994)</td>
<td>355</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>50/100/200mg</td>
<td>324</td>
<td>12 weeks</td>
<td>NO</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20/40/60mg</td>
<td>348</td>
<td>12 weeks</td>
<td>YES</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20/40/60mg</td>
<td>352</td>
<td>12 weeks</td>
<td>YES</td>
</tr>
<tr>
<td>Montgomery et al (2001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10/20mg</td>
<td>457</td>
<td>12 weeks</td>
<td>YES</td>
</tr>
<tr>
<td>Stein et al 2007</td>
<td></td>
<td></td>
<td>24 weeks</td>
<td>YES</td>
</tr>
</tbody>
</table>

1 marginally significant benefit for medium and higher doses on primary analysis (total Y-BOCS; p = 0.059); significant on ‘responder’ analysis (p<0.05).

2 60mg significantly better than placebo and 20mg on secondary analyses
Dose-titration

• address common concerns about taking medication with the patient e.g. potential side effects including worsening anxiety

• explain that OCD responds to drug treatment in a slow and gradual way and that improvements may take weeks or months

• Start with standard antidepressant dose and titrate upwards slowly according to clinical response toward remission
Definitions of remission and recovery for OCD

Remission is a period during which sufficient improvement has occurred that the individual no longer has syndromal OCD.

Remission = YBOCS < 16
OR YBOCS ≤ 12
OR YBOCS ≤ 10
OR YBOCS ≤ 7

(Simpson et al., 2006, Stein et al 2007)

Recovery is a sustained period of remission (? >6 months)

Includes moving forward and rebuilding one’s life and incorporating improvements in areas such as quality of life and psychosocial function.
Patients in remission (Y-BOCS ≤ 10)


* p<0.05 vs PBO, ** p<0.01 vs PBO

Stein et al. Poster presented at APA 2006
Does SSRI improve health related disability and quality of life?
Mean baseline SF-36 scores for each of 8 dimensions (pooled FAS n = 921) in comparison to published U.S. norms and baseline data from two published studies of impact of OCD on SF-36 scores.
Mean change in SF-36 from baseline to end of double-blind period (OC, ANCOVA)

- Physical Functioning
- Role-Physical
- Bodily Pain
- General Health
- Vitality
- Social Functioning
- Role-Emotional
- Mental Health

* p<0.05 vs PBO, ** p<0.01 vs PBO, *** p<0.001 vs PBO
Does adding CBT improve outcomes?
Does adding CBT to SRI improve outcomes?  
Randomised Studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DURATION (weeks)</th>
<th>OUTCOME</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rachman et al (1979)²⁷</td>
<td>3</td>
<td>CMI+EXP = CMI+REL</td>
<td>OC scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CMI+EXP = PLAC+EXP</td>
<td>No ITT</td>
</tr>
<tr>
<td>Marks et al (1980)²⁸</td>
<td>8</td>
<td>CMI+EXP &gt; PLAC+EXP</td>
<td>Rituals &amp; depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No ITT</td>
</tr>
<tr>
<td>Cottraux et al (1990)²⁹</td>
<td>24</td>
<td>FLV+EXP &gt; PLAC+EXP</td>
<td>Rituals &amp; depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No ITT</td>
</tr>
<tr>
<td>Hohagen et al (1998)³⁰</td>
<td>9</td>
<td>FLV+CBT &gt; PLAC+CBT</td>
<td>Multimodal CBT</td>
</tr>
<tr>
<td>Foa et al (2005)³¹</td>
<td>12</td>
<td>CMI+ERP &gt; CMI &gt; PLAC</td>
<td>No ERP control</td>
</tr>
<tr>
<td>Tenneij et al (2006)³²</td>
<td>52</td>
<td>SSRI+CBT &gt; SSRI</td>
<td>12 wk SRI responders</td>
</tr>
</tbody>
</table>

Three controlled studies suggest adding SRI to CBT improves outcome over CBT given alone.

One controlled study suggests adding ERP to SSRI improves outcome over SSRI given alone (in partially SRI-resistant OCD).
OCD of at least moderate severity despite a therapeutic SRI dose≤ 12 wk.
SSRI+Risperidone n = 40; SSRI+EX/RP n = 40; SSRI+ placebo n = 20.
N=86 (86%) completed the trial.
EX/RP= 17 twice-weekly 90-minute sessions, daily homework (at least 1 hour of self-directed exposures daily), and between session telephone check-ins.

Change in Symptom Severity During Augmentation

SSRI+ERP
SSRI+RISP
SSRI+PLAC

Week0  Week4  Week8
Change in Symptom Severity During Augmentation
How long to remain on treatment?
Definitions of relapse for OCD

Relapse = Y-BOCS worsened by 25%
  by 50%
  by 100%
  by 5 points

Y-BOCS ≥ 20
CGI-I = 6
CGI-S worsened by 1 point

Using different methodologies and criteria, relapse rates following drug discontinuation range from 24% over 28 weeks (Koran et al 2002) to 89% over 7 weeks (Pato et al 1988).

Esc vs placebo: Time to relapse

Fineberg et al. Eur Neuropsychopharmacol. 2007

ESC N=163; Relapses: 38 (23.5%)
PBO N=157; Relapses: 81 (52.6%)
Hazard ratio = 2.74

Log-rank test: $p < 0.001$ ***
### Double-blind studies of relapse prevention in OCD

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DRUG</th>
<th>Duration prior drug treatment</th>
<th>n in discont. phase</th>
<th>Follow-up after discont.</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romano et al (1998)</td>
<td>fluoxetine</td>
<td>20 weeks</td>
<td>71</td>
<td>52 wks</td>
<td>Relapse rate on plac = pooled fluox Relapse rate on plac &gt; fluox 60mg</td>
</tr>
<tr>
<td>Koran et al (2002)</td>
<td>sertraline</td>
<td>52 weeks</td>
<td>223</td>
<td>28 wks</td>
<td>Relapse rate on plac = sert Acute exacerb of OCD on plac &gt; sert Dropout due to relapse on plac &gt; sert</td>
</tr>
<tr>
<td>bGeller et al (2003)</td>
<td>paroxetine</td>
<td>16 weeks</td>
<td>193</td>
<td>16 wks</td>
<td>Relapse rate on plac = parox</td>
</tr>
<tr>
<td>Hollander et al (2003)</td>
<td>paroxetine</td>
<td>12 weeks</td>
<td>105</td>
<td>36 wks</td>
<td>Relapse rate on plac &gt; parox</td>
</tr>
<tr>
<td>Fineberg et al (2006)</td>
<td>escitalopram</td>
<td>16 weeks</td>
<td>322</td>
<td>24 wks</td>
<td>Time to relapse on esc &gt; plac Relapse rate on plac &gt; esc</td>
</tr>
</tbody>
</table>

b: in children and adolescents
Meta-analysis of SSRI relapse prevention studies in adults with OCD
Fineberg et al Int Clin Psychopharmacol 2007

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>Weight %</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romano 2001</td>
<td>7/36</td>
<td>11/34</td>
<td>8.31 [0.28, 1.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koran 2002</td>
<td>3/100</td>
<td>8/114</td>
<td>2.65 [0.16, 2.59]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollander 2003</td>
<td>26/53</td>
<td>30/51</td>
<td>32.72 [0.42, 0.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fineberg 2006</td>
<td>36/163</td>
<td>81/187</td>
<td>56.12 [0.33, 0.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>360</td>
<td>356</td>
<td>100.00 [0.41, 0.66]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 88 (Treatment), 127 (Control)
Test for heterogeneity: Ch^2 = 1.94, df = 3 (P = 0.58), I^2 = 0%
Test for overall effect: Z = 5.34 (P < 0.0001)
Mean SF-36 scores at last assessment for relapsed (n=119) and non-relapsed (n=201) patients (relapse-prevention study). (Hollander E et al, J Clin Psychiatry, Jun;71(6):784-92. 2010.)

p<0.05, **p<0.01, ***p<0.001 vs. placebo (ANCOVA)
Sustained Response Versus Relapse: The Pharmacotherapeutic Goal For OCD.

Fineberg NA et al Int Clin Psychopharmacol 2007

• “OCD is a chronic disorder. On the basis of current evidence, long-term treatment with SSRIs is indicated to protect against relapse for most cases and treatment should not be discontinued.

• Clinicians need to inform their patients about the risks of relapse, so that collaborative decisions about maintenance treatment can be agreed.”
Definitions of treatment non-response and resistance

Depends on dose and duration of treatment

Non-response = <25% improvement in Y-BOCS

(T pallanti et al 2002, simpson et al 2006)

Treatment-resistance = non-response to *two trials* of 12 weeks SRI at therapeutic dose

(Fineberg et al 2007)
SRI-resistant OCD: Predictors of non-response

**Adults**
- Longer illness duration
- Early age of onset
- Chronic course
- Compulsive rituals
- Comorbid tics
- Comorbid PD (OCPD)
- Previous SRI treatment
- Sub-clinical depression
- Hoarding

**Children**
- Comorbid ADHD
- Comorbid tics
- Comorbid oppositional defiant disorder
- Comorbid autism

Large scale prospective longitudinal studies of response-predictors

- Venlafaxine- response associated with S/L genotype of 5-HTTLPR polymorphism;
Comorbidity in UK refractory OCD; cross sectional survey of systematic data. N=25

<table>
<thead>
<tr>
<th>Disorder</th>
<th>n</th>
<th>Disorder</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS</td>
<td>5</td>
<td>BPD</td>
<td>2</td>
</tr>
<tr>
<td>Tic disorder</td>
<td>5</td>
<td>Anorexia N</td>
<td>2</td>
</tr>
<tr>
<td>Aspergers</td>
<td>5</td>
<td>SAD</td>
<td>2</td>
</tr>
<tr>
<td>OCPD</td>
<td>3</td>
<td>Depression</td>
<td>2</td>
</tr>
<tr>
<td>Trich/skin picking</td>
<td>3</td>
<td>BDD</td>
<td>1</td>
</tr>
<tr>
<td>Bipolar AD</td>
<td>3</td>
<td>Schizotypal</td>
<td>1</td>
</tr>
<tr>
<td>Depersonalisation</td>
<td>2</td>
<td>Alcohol dep</td>
<td>1</td>
</tr>
</tbody>
</table>
Do specific OCD symptoms predict treatment-response?
Symmetry/Hoarding predicts poor outcome to escitalopram.

- 466 OCD patients in an 12 week RCT of escitalopram.

- Exploratory factor analysis of individual Y-BOCS items yielded 5 factors (contamination/cleaning, harm/checking, hoarding/symmetry, religious/sexual, and somatic/hypochondriacal).

- Analyses of covariance for overall group demonstrated escitalopram more effective than placebo.

- A significant interaction for “hoarding/symmetry” was associated with a poorer treatment response (p<0.001).

- Hoarding/symmetry may characterise an early-onset group of OCD patients, with involvement of neurotransmitters other than serotonin.

- Further work is needed to delineate of OCD subtypes and their underlying neurobiology and treatment responsivity.
SRI-resistant OCD: a pharmacological algorithm

**First-line treatment**
SSRI, maximal dose, 12 weeks

**Switch SSRI or clomipramine, maximal dose, 12 weeks**

**Increase dose beyond formulary limits**

**Add second generation antipsychotic**

**Add haloperidol**

**Intravenous SSRI or clomipramine**

**Combine clomipramine and SSRIs**

**Novel agents**

*Review diagnosis*
Switching SSRIs in OCD.

• Delay switching until at least 12 weeks (March et al 1997)

• 11-33% patients not responding to one SSRI show a clinically meaningful response to another, with declining likelihood of subsequent response to other agents (Fineberg et al 2006)

• Two small open label studies suggesting benefit from a change to venlafaxine (Hollander et al 2002, 2003) and one to duloxetine (Dell Osso et al 2008) were counterbalanced by a double-blind study showing a significantly more favourable response for patients switched from venlafaxine to paroxetine (56%) than vice versa (19%) (Denys et al 2004).
SRI-resistant OCD: a pharmacological algorithm

First-line treatment
SSRI, maximal dose, 12 weeks

Switch SSRI or clomipramine, maximal dose, 12 weeks

Increase dose beyond formulary limits
Add second generation antipsychotic

Add haloperidol
Intravenous SSRI or clomipramine
Combine clomipramine and SSRIs

Novel agents
Randomised controlled studies in SRI-Resistant OCD

Appear effective:
- Adding haloperidol\textsuperscript{b}
- Adding risperidone
- Adding quetiapine
- Adding olanzapine
- Adding aripiprazole
- High dose sertraline
- Intravenous clomipramine\textsuperscript{a}

\textbf{Apparently ineffective:}
- Adding lithium, topiramate
- Adding buspirone
- Adding triiodothyronine (lithothyronine)
- Adding desipramine
- Adding inositol
- Adding clonazepam
- Adding naltrexone
- Adding oxytocin

\textsuperscript{a} Remains investigational in many countries
\textsuperscript{b} Primarily in 'tic-related' OCD
Higher-dose SSRI monotherapy for resistant OCD?  
Ninan et al J Clin Psych 2006

- 66 OCD non-responders to 16 weeks of sertraline, randomly assigned:

- 12 weeks high-dose sertraline (250-400 mg/day, mean = 357mg, N = 30) showed significantly greater improvement than 200mg/day (N = 36) on YBOCS, NIMH Global OC Scale, CGI-I.

- Responder rates not significantly different between groups, either on completer analysis (34% vs. 52%) or endpoint analysis (33% vs. 40%).

- Both treatments showed similar adverse event rates.

- Higher than labelled SSRI doses may be a treatment option for OCD patients who fail to respond to standard acute treatment.
<table>
<thead>
<tr>
<th>SRI</th>
<th>Usual Max Dose (mg/day)</th>
<th>Occasionally Prescribed Max Dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram</td>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>clomipramine</td>
<td>250</td>
<td>-</td>
</tr>
<tr>
<td>escitalopram</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>300</td>
<td>450</td>
</tr>
<tr>
<td>paroxetine</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>sertraline</td>
<td>200</td>
<td>400</td>
</tr>
</tbody>
</table>

High-dose SSRIs in OCD: a systematic retrospective case notes survey of 192 outpatients.
Pampaloni I et al J Psychopharm. Epub. April 7th 2009

- 26 (13.5%) received high-dose SRI for 3–364 wks (mean 81.5 wks)

- At the last assessment, high-dose SSRI showed sig. within-group improvements from baseline (Y-BOCS 25.4 vs. 21.0)

- Endpoint scores for the high-dose group remained sig. higher than controls treated for a matched period (Y-BOCS 21.0 vs. 15.5), suggesting they showed enduring treatment-resistance.

- Frequency of AEs (@50%) did not sig. differ between high and non-high dose groups. Severe AEs observed in one case with ASD.

- Sustained high-dose SRI was associated with clinical improvement and was well-tolerated in a particularly refractory OCD sample.

- AE monitoring advisable, with special care in comorbid cases.
Antipsychotics as monotherapy in OCD

- Early open-label studies with first generation antipsychotics fail modern standards for clinical trial methodology (e.g., Trethowan and Scott 1955, Altschuler 1962, Hussein and Ahad 1970, O’Regan 1970, Rivers-Bulkeley and Hollender 1982).

- Open-label clozapine was ineffective in 12 SRI-resistant cases (McDougle et al. 1995b).

- Open-label aripiprazole was ineffective in 7 cases including SRI-naive and resistant individuals (Connor et al. 2005).
Antipsychotic augmentation of SRIs in resistant OCD


<table>
<thead>
<tr>
<th>Study or variable</th>
<th>Treatment</th>
<th>Control</th>
<th>RR (random)</th>
<th>Weight</th>
<th>RR (random)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/n</td>
<td>n/n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haloperidol</td>
<td>2/17</td>
<td>0/17</td>
<td>6.46</td>
<td>23.00</td>
<td>1.46, 341.59</td>
<td>1994</td>
</tr>
<tr>
<td>risperidone</td>
<td>4/10</td>
<td>2/19</td>
<td>2.72</td>
<td>1.99</td>
<td>0.63, 20.00</td>
<td>2004</td>
</tr>
<tr>
<td>olanzapine</td>
<td>4/10</td>
<td>0/4</td>
<td>6.33</td>
<td>5.13</td>
<td>0.28, 99.82</td>
<td>2003</td>
</tr>
<tr>
<td>quetiapine</td>
<td>4/10</td>
<td>0/4</td>
<td>6.33</td>
<td>5.13</td>
<td>0.28, 99.82</td>
<td>2003</td>
</tr>
</tbody>
</table>

Favours control

Favours treatment

Figure 2: Response rate ratios of antipsychotic augmentation overall compared with Placebo.
8-week, single-blind, randomized trial comparing risperidone (1-3mg) versus olanzapine (2.5-10mg) augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder.


- N = 50
- Significant within-group improvements in both groups
- No differences between the two treatment groups
- No differences emerged for the proportion of patients reporting at least one adverse event
- Profiles of adverse experiences differed significantly; risperidone associated with amenorrhoea and olanzapine with weight gain.
Who is responsible for care?

STEP 1 Individuals, public organisations, NHS

STEP 2 GPs, practice nurses, school health advisors

STEP 3 GPs and primary care team, primary care mental health worker, family support team.

STEP 4 Local multidisciplinary care (GP or psychiatrist).

STEP 5 Multidisciplinary teams with specific expertise in management of OCD (regional).

STEP 6 Inpatient care or intensive treatment programmes (national).
Does intensive CBT (ERP plus cognitive restructuring) improve severe, refractory OCD? A 24 week naturalistic study of 52 inpatients.

Significant within-group differences between total Y-BOCS scores at admission, 12 weeks, and 24 weeks (ANOVA; $P<.001$).

Follow-up comparisons between consecutive measurements demonstrated significant falls in total Y-BOCS scores from admission to 12 weeks ($P<.001$) and between the 12-week and 24-week assessments ($P<.001$).
SRI-resistant OCD: a pharmacological algorithm

First-line treatment
SSRI, maximal dose, 12 weeks

Switch SSRI or clomipramine, maximal dose, 12 weeks

Increase dose beyond formulary limits
Add second generation antipsychotic

Add haloperidol
Intravenous SSRI or clomipramine
Combine clomipramine and SSRIs

Novel agents
Intravenous SSRI / clomipramine?

• Pulse loading with IV (but not oral) clomipramine produced an early and rapid decrease in symptoms but the advantage was not sustained (Koran et al 1997)

• Two double blind trials supported the efficacy of IV clomipramine in resistant OCD (Fallon et al 1998, Koran et al 1997)

• An open label study of IV citalopram hinted at efficacy (Pallanti et al 2002)
Combine clomipramine and SSRI?

• Caution is required if clomipramine is combined with SSRIs that potentially interact at the hepatic microsomes.

• Clomipramine plasma levels and ECG monitoring are usually recommended

• Citalopram, escitalopram and to a lesser extent sertraline may be less likely to interact and therefore to be preferred.

• An open label study of citalopram with clomipramine (Pallanti et al 1999) requires replication under controlled conditions.
**SRI-resistant OCD: a pharmacological algorithm**

1. **First-line treatment**
   - SSRI, maximal dose, 12 weeks

2. **Switch SSRI or clomipramine, maximal dose, 12 weeks**

3. **Increase dose beyond formulary limits**
   - Add second generation antipsychotic

4. **Add haloperidol**

5. **Intravenous SSRI or clomipramine**

6. **Combine clomipramine and SSRIs**

7. **Novel agents**

---

*Review diagnosis*
<table>
<thead>
<tr>
<th>Compound</th>
<th>Study</th>
<th>Study design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-amphetamine (single dose)</td>
<td>Insel et al 1983</td>
<td>Double blind RCT</td>
<td>D-amphet &gt; placebo</td>
</tr>
<tr>
<td></td>
<td>Joffe et al 1991</td>
<td></td>
<td>D-amphetamine &gt; placebo; methylphenidate = placebo</td>
</tr>
<tr>
<td>Buproprion</td>
<td>Vulink et al 2005</td>
<td>Open-label</td>
<td>D-amphet &gt; placebo; methylphenidate = placebo</td>
</tr>
<tr>
<td>Ketamine (IV) (single dose)</td>
<td>Bloch et al (2012)</td>
<td>Open-label</td>
<td>No responders at 3d</td>
</tr>
<tr>
<td></td>
<td>Rodriguez et al 2013</td>
<td>Double-blind RCT</td>
<td>Ketamine &gt; placebo; 7d</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Koran LM et al 2005</td>
<td>Double-blind discontin</td>
<td>MIR &gt; placebo</td>
</tr>
<tr>
<td>D-cycloserine &amp; CBT</td>
<td>Storch et al 2007</td>
<td>D-cyc + BT vs pla + BT</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Kushner et al 2007</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Wilhelm et al 2008</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>D-amphetamine + SSRI vs caffeine + SSRI</td>
<td>Koran et al 2009</td>
<td>Double-blind RCT</td>
<td>&gt;50% Responders in both groups at 1 wk</td>
</tr>
<tr>
<td>Topiramate + SSRI</td>
<td>Berlin HA et al 2010</td>
<td>Double-blind RCT</td>
<td>Compulsions sig, Total Y-BOCS NS</td>
</tr>
<tr>
<td>Memantine + SRI</td>
<td>Haghigi et al 2013</td>
<td>Double-blind RCT</td>
<td>Memantine &gt; placebo</td>
</tr>
<tr>
<td>N acetyl cysteine</td>
<td>Afshar et al 2012</td>
<td>Double-blind RCT</td>
<td>N AC &gt; placebo</td>
</tr>
</tbody>
</table>
Somatic treatments in highly refractory OCD.

**ECT:** Insufficient evidence to recommend ECT for OCD, given potential associated risks (APA Practice Guidelines on OCD; Koran et al 2007).

**rTMS:** A systematic review of rTMS studies in OCD (1996 – 2010; Jaafari et al 2012) and a meta-analysis (Berlim et al 2013) suggest promising results in comparison to sham rTMS with target areas such as orbitofrontal cortex and supplementary motor area. *Though promising, rTMS remains experimental.*

**DBS:** stimulating ventral striatum/ventral capsule or subthalamic nucleus may produce therapeutic effects by modulating the cortico-striatal neurocircuity that is widely proposed to mediate OCD (Bourne et al 2012). *Though promising, DBS remains experimental.*

**Ablative neurosurgery:** (ant. cingulotomy, ant. capsulotomy) remains the last resort for very severely ill patients who do not respond to expert delivered trials of pharmacotherapy and CBT of optimal dosage/content, duration, and mode of delivery as assessed by experienced experts in specialty treatments for OCD.
Neurosurgery for OCD: Inclusion criteria

1. Legal status: both patients detained under the mental health act and those who voluntarily seek treatment can be considered.

2. Confirmation of diagnosis: individuals will normally fulfill criteria for a primary diagnosis according to ICD-10 F42.0-F42.9. Individuals with treatment-refractory obsessional and/or compulsive symptoms in the presence of other comorbid mental disorder (e.g. depression, schizophrenia) can be considered for surgery but additional criteria for adequacy of treatment will be applied.

3. Duration of illness: an absolute minimum of 3 years, with at least 2 years of unremitting symptoms despite intensive psychopharmacological and psychological treatment. Only in exceptional circumstances would a duration of illness of <5 years be considered.

4. Consent: the patient must be considered capable of providing sustained, informed consent.

5. Age>20 years
Neurosurgery for OCD; Exclusion criteria

1. Age <20 years.
2. Failure to fulfill ICD-10 criteria for F42.0-F42.9.
3. Incapacity to give informed consent.
4. A current diagnosis of substance misuse fulfilling criteria for ICD-10 F10-F19, ‘Mental and behavioural disorders due to psychoactive substance use’.
5. A diagnosis of organic brain syndrome fulfilling criteria for ICD-10 F00-F09, including Alzheimer’s disease, vascular and other dementias.
6. A diagnosis of disorder of adult personality fulfilling criteria for ICD-10 F60-F69.
7. A diagnosis of pervasive developmental disorder fulfilling criteria for ICD-10 F84.
Conclusions

• Treatment effect on SSRI partial and dose and time dependent

• Long-term SSRI protects against relapse

• Combining SSRI + ERP may confer added benefit

• Treatment resistance is poorly understood and may require specialised teams.

• Developing role for antipsychotics

• New, more highly effective treatments targeting core symptoms desirable
International College of Obsessive Compulsive Spectrum Disorders (ICOCS)

Committee: J Menchon (Chair)
N. Fineberg (Sec)
M Figee
E. Hollander
C Ruck
R Shavitt
D. Stein
J. Zohar

www.ICOCS.org
Opiate agonist and antagonists in OCD

• Morphine > placebo in a 2-week, randomised double-blind crossover study of once weekly oral morphine, lorazepam and placebo\(^1\).

• 2 randomised trials showed lack of efficacy or \textit{worsening} on naltrexone \(^2,3\),

\(^1\)Koran L et al (2005)
\(^2\)Keuler et al (1996)
\(^3\)Amiaz R et al (2008)
N-methyl D-aspartate (NMDA)-receptors, glutamate and OCD

• NMDA receptors important for neurodevelopment, synaptic plasticity and excito-toxicity.

• Postsynaptic NMDA receptors activated by glutamate only in presence of co-transmitters glycine, d-serine.

• Elevated glutamate in caudate, and reduced glutamate in ACC on MRS in OCD (Rosenberg DR et al., 2004)

• Abnormally high glutamatergic concentrations in children with OCD decreased in line with symptom severity during SSRI treatment (Rosenberg DR, et al. 2000).


Method
10 OCD and 7 GAD subjects received 12 weeks open-label memantine 10 mg BD, as monotherapy or augmentation of existing medication.

Results: At endpoint

OCD - significant reduction in YBOCS (mean 40.6%, \( p < 0.001 \)).
3/10 OCD subjects classified as responders, and 7 / 10 experienced a \( \geq 45\% \) reduction in Y-BOCS.

GAD - reduction in HARS scores (mean 22.4%, \( p = 0.012 \)). No responders, and none experienced a \( \geq 50\% \) reduction in HARS.

Memantine was well tolerated, and there were no serious AEs

Conclusions: Memantine may have preferential efficacy in OCD vs. GAD.
### Does D-cycloserine improve CBT outcomes in OCD?

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Duration (wk)</th>
<th>design</th>
<th>Outcome on D-cyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storch et al 2007</td>
<td>24</td>
<td>12 weekly BT sessions</td>
<td>D-cyc 250mg (+4h) + BT vs. plac + BT</td>
<td>NS</td>
</tr>
<tr>
<td>Kushner et al 2007</td>
<td>25</td>
<td>10 twice-weekly BT sessions</td>
<td>D-cyc 125mg (+2h) + BT vs. plac + BT</td>
<td>NS (at S4; sig improvement in distress)</td>
</tr>
<tr>
<td>Wilhelm et al 2008</td>
<td>23</td>
<td>10 twice-weekly BT sessions</td>
<td>D-cyc 100mg (+1h) + BT vs. plac +BT</td>
<td>D-cyc&gt;plac on Y-BOCS at S5 and on BDI at S10, but not at 1 month</td>
</tr>
</tbody>
</table>
Cognitive Enhancers – a role in OCD?

**D-Amphetamine:**
- Two placebo-controlled single-dose studies (n=12, n=11) showed improvement on CPRS-OCS. One study showed improvements on an attentional task.

**Methylphenidate:**
- A placebo controlled single-dose study (n=12) showed no effect on CPRS-OCS.
- One case report of OCD worsening with methylphenidate treatment (but not with d-amphetamine).
- Another report of emergence of OC symptoms in 3 cases.

**Modafinil:**
- 2 reports of cases: exacerbation of obsessions in 2 patients with SRI-responsive OCD; dose-related exacerbation of anxiety and improvement in an attentional task in one SRI-resistant OCD case

Conclusions

• Treatment effect on SSRI partial and dose and time dependent

• Long-term SSRI protects against relapse

• Combining SSRI + ERP may confer added benefit

• New, more highly effective treatments targeting core symptoms desirable
“Beckham said: 'I have got this obsessive compulsive disorder where I have to have everything in a straight line or everything has to be in pairs.' 'I'll put my Pepsi cans in the fridge and if there's one too many then I'll put it in another cupboard somewhere.'

Beckham reportedly spends hours straightening the furniture, apparently buys exactly 20 packets of Super Noodles on each visit to the supermarket and wears a new pair of football boots for every match. His wife Victoria, 31, has said: 'Everything has to match in the house. If there are three cans of Diet Pepsi, he'd throw one away because it's uneven.'"
<table>
<thead>
<tr>
<th>Common obsessions</th>
<th>Common compulsions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of causing harm to someone</td>
<td>A. Behaviours</td>
</tr>
<tr>
<td>Fear of self-harm</td>
<td>Cleaning</td>
</tr>
<tr>
<td>Fear of behaving unacceptably</td>
<td>Hand washing</td>
</tr>
<tr>
<td>Fear of contamination</td>
<td>Checking</td>
</tr>
<tr>
<td>Fear of making a mistake</td>
<td>Asking for reassurance</td>
</tr>
<tr>
<td>Need for symmetry or exactness</td>
<td>Ordering and arranging</td>
</tr>
<tr>
<td></td>
<td>Hoarding</td>
</tr>
<tr>
<td></td>
<td>B. Mental acts</td>
</tr>
<tr>
<td></td>
<td>Counting</td>
</tr>
<tr>
<td></td>
<td>Making mental lists</td>
</tr>
<tr>
<td></td>
<td>Repeating words silently</td>
</tr>
</tbody>
</table>
### Anxiety disorders – epidemiology

(Wittchen & Jacoby, Eur Neuropsychopharmacol 2005)

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>12-month estimate % (95% CI)</th>
<th>Lifetime estimate % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (without PTSD)</td>
<td>12.0 (11.1 – 13.0)</td>
<td>21.1 (20.5 – 21.6)</td>
</tr>
<tr>
<td>Panic Disorder (+/- agoraphobia)</td>
<td>2.3 (1.9 – 2.8)</td>
<td>3.8 (3.1 – 4.5)</td>
</tr>
<tr>
<td>Agoraphobia (without panic)</td>
<td>2.0 (1.7 – 2.5)</td>
<td>3.8 (3.1 – 4.5)</td>
</tr>
<tr>
<td>GAD</td>
<td>1.5 (1.2 – 1.9)</td>
<td>5.1 (4.3 – 5.9)</td>
</tr>
<tr>
<td>Social Anxiety Disorder</td>
<td>2.0 (1.6 – 2.5)</td>
<td>5.8 (5.1 – 6.5)</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>7.6 (6.9 – 8.5)</td>
<td>13.2 (12.8 – 13.6)</td>
</tr>
<tr>
<td>OCD</td>
<td>0.7 (0.5 – 1.0)</td>
<td>0.8 (0.6 – 1.1)</td>
</tr>
<tr>
<td>PTSD</td>
<td>1.2 (0.9 – 1.3)</td>
<td>Not established</td>
</tr>
</tbody>
</table>
Age at onset of OCD

![Graph showing the age at onset of OCD for males and females.](image-url)
Aetiology of OCD: cognitive theories

(Beck A. Arch Gen Psych 2005):

Biassed information processing leads to overestimation of threat (cognitive distortion).

Danger-oriented cognitive schemas predispose individuals to narrow their attention to threat, make catastrophic interpretations of ambiguous stimuli and engage in dysfunctional ‘safety behaviours’ eg compulsions, avoidance

- Irrational thoughts and beliefs inadequately challenged by OCD patients (Ellis, 1962)
- Overinflated ideas of personal responsibility (Salkovskis, 1999)
- Exaggerated danger expectancies (Menzies et al., 2000)
Thought- action fusion
Rachman (1976)

• Inflated sense of responsibility may derive from false assumptions about thoughts and actions, eg:
  - Having a thought about an action is equivalent to doing the action
  - Failing to prevent harm is the same as causing harm
  - Failing to neutralise an aggressive obsession is tantamount to wanting to harm others
  - One should control one’s thoughts

• Supportive evidence: sense of responsibility predicted level of distress over obsessions (Scarabelotti et al 1995) and reducing responsibility lessened distress and urge to ritualise (Ladouceur et al 1995).

• However, some question over the link between responsibility and OCD (Freeston et al 1993)
Aetiology of OCD: behavioural theories
Marks I, 1969, Rachman and Hodgson 1980

- Obsessions are anxiogenic
- Compulsions are anxiolytic
- Anxiety is a re-inforcer

Solomon R (1953):
Dog + shock + light → anxiety → escape
Dog + light → anxiety → escape (ritual/avoidance)
Dog + light → anxiety → no escape (ERP) → extinction


Distress about intrusive cognitions appears linked to attempts to remove them (Freeston M et al 1991)
Behavioural Theories of OCD

Anxiety

Time

- Feeling "contaminated"
- Ritualisation
- Anxiety reduces
  - only a little
  - not for long

Anxiety rises
### Rates of clinical response in placebo controlled studies of SSRIs for patients with OCD

<table>
<thead>
<tr>
<th>DRUG [duration weeks]</th>
<th>DEFINITION OF CLINICAL RESPONSE</th>
<th>STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>60mg [8]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60mg [13]</td>
<td></td>
<td>Zohar and Judge (1996)</td>
</tr>
<tr>
<td>Fluoxetine [16]</td>
<td>57%</td>
<td>Stein et al 2007</td>
</tr>
<tr>
<td>Paroxetine [12]</td>
<td>55.1% 55.3%</td>
<td></td>
</tr>
<tr>
<td>Clomipramine [12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram 20mg [12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40mg [12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60mg [12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram 20m [24]</td>
<td>70.2% 67.2%</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 40mg [24]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Escitalopram 10mg, 20mg vs paroxetine 40mg and placebo: 24 weeks study.
<table>
<thead>
<tr>
<th>Drug (duration, wk)</th>
<th>Study</th>
<th>n</th>
<th>Dose (mg/day) [mean dose]</th>
<th>Response criteria</th>
<th>Response rate on active drug</th>
<th>Placebo response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>McDougle et al. (2000)(^{47})</td>
<td>36</td>
<td>1 titrated to 6 as tolerated [2.2]</td>
<td>Marked=3 of a,c,e Partial=2 of a,c,e</td>
<td>4/18 (22%) 5/18 (28%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Hollander et al. (2003)(^{48})</td>
<td>16</td>
<td>0.5-3.0</td>
<td>b, d</td>
<td>4/10 (40%)</td>
<td>0/6 (0%)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Li et al. (2005)(^{49})</td>
<td>16</td>
<td>1</td>
<td>not defined</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Bystritsky et al. (2004)(^{50})</td>
<td>26</td>
<td>up to 20 [11.2]</td>
<td>b</td>
<td>6/13 (46%)</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Shapira et al. (2004)(^{51})</td>
<td>44</td>
<td>5-10 [6.1]</td>
<td>not defined</td>
<td>5/22 (23%)(^{a}) 9/22 (41%)(^{b})</td>
<td>4/22 (18%)(^{a}) 9/22 (41%)(^{b})</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Denys et al. (2004)(^{52})</td>
<td>40</td>
<td>300</td>
<td>a, d</td>
<td>8/20 (40%)</td>
<td>2/20 (10%)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Carey et al. (2005)(^{53})</td>
<td>41</td>
<td>300</td>
<td>b, d</td>
<td>8/20 (40%)</td>
<td>10/21 (47%)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Fineberg et al. (2005)(^{54})</td>
<td>21</td>
<td>400 [215]</td>
<td>b</td>
<td>3/11 (27%)</td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Kordon et al. (2008)(^{55})</td>
<td>40</td>
<td>400-600</td>
<td>a</td>
<td>6/20 (33%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Vulink et al. (2009)(^{56})</td>
<td>76</td>
<td>300-450</td>
<td>a, d</td>
<td>22/39 (56%)</td>
<td>15/37 (41%)</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Muscatello et al. (2011)</td>
<td>40</td>
<td>15</td>
<td>a, b</td>
<td>7 (35%), 11 (55%)</td>
<td>0/20 (0%)</td>
</tr>
</tbody>
</table>

\(^{a}\) \(\geq\)35% improvement in YBOCS; \(^{b}\) \(\geq\)25% improvement in YBOCS; \(^{c}\) Final YBOCS score <16; \(^{d}\) CGI of “much improved” or “very much improved”; \(^{e}\) consensus opinion of investigators
Open-label, high-dose escitalopram in resistant OCD
Rabinowitz I et al., Int J Psychopharmacol 2008

• 67 patients received escitalopram 10-20 mg/day for 4 weeks,

• 64 patients who did not achieve a > or =25% Y-BOCS reduction from baseline continued on higher doses of escitalopram (mean dose, 33.8 mg/day; maximum 50 mg/day) for 12 weeks.

• At endpoint, high-dose escitalopram had significantly improved the OCD symptoms (Y-BOCS score) and all the other efficacy measures (P<0.001), compared with baseline.

• Escitalopram was also well tolerated, with no discontinuations during the 12-week high-dose phase. The only reported adverse drug reactions were dry mouth (n=8, 12.1%) and decreased sexual desire (n=21, 31.8%).

• Randomized, blinded studies are needed to reinforce these findings.
Cognitive-Behavioral Therapy vs Risperidone for Augmenting Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder: A Randomized Clinical Trial.


Source
Department of Psychiatry, Columbia University, New York, New York2New York State Psychiatric Institute, New York, New York.

Abstract
IMPORTANCE Obsessive-compulsive disorder (OCD) is one of the world's most disabling illnesses according to the World Health Organization. Serotonin reuptake inhibitors (SRIs) are the only medications approved by the Food and Drug Administration to treat OCD, but few patients achieve minimal symptoms from an SRI alone. In such cases, practice guidelines recommend adding antipsychotics or cognitive-behavioral therapy consisting of exposure and ritual prevention (EX/RP). OBJECTIVE To compare the effects of these 2 SRI augmentation strategies vs pill placebo for the first time, to our knowledge, in adults with OCD. DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial (conducted January 2007-August 2012) at 2 academic outpatient research clinics that specialize in OCD and anxiety disorders. Patients (aged 18-70 years) were eligible if they had OCD of at least moderate severity despite a therapeutic SRI dose for at least 12 weeks prior to entry. Of 163 who were eligible, 100 were randomized (risperidone, n=40; EX/RP, n=40; and placebo, n=20), and 86 completed the trial. INTERVENTIONS While continuing their SRI at the same dose, patients were randomized to the addition of 8 weeks of risperidone (up to 4 mg/d), EX/RP (17 sessions delivered twice weekly), or pill placebo. Independent assessments were conducted every 4 weeks. MAIN OUTCOME AND MEASURE The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) to measure OCD severity. RESULTS Patients randomized to EX/RP had significantly greater reduction in week 8 Y-BOCS scores based on mixed-effects models (vs risperidone: mean [SE], -9.72 [1.38]; P < .001 vs placebo: mean [SE], -10.10 [1.68]; P < .001). Patients receiving risperidone did not significantly differ from those receiving placebo (mean [SE], -0.38 [1.72]; P = .83). More patients receiving EX/RP responded (Y-BOCS score decrease ≥25%: 80% for EX/RP, 23% for risperidone, and 15% for placebo; P < .001). More patients receiving EX/RP achieved minimal symptoms (Y-BOCS score ≤12: 43% for EX/RP, 13% for risperidone, and 5% for placebo; P = .001). Adding EX/RP was also superior to risperidone and placebo in improving insight, functioning, and quality of life. CONCLUSIONS AND RELEVANCE Adding EX/RP to SRIs was superior to both risperidone and pill placebo. Patients with OCD receiving SRIs who continue to have clinically significant symptoms should be offered EX/RP before antipsychotics given its superior efficacy and less negative adverse effect profile. TRIAL REGISTRATION clinicaltrials.gov Identifier:
Antipsychotic augmentation for treatment resistant OCD: what if antipsychotic is discontinued?

- Retrospective chart review of 18 OCD patients who responded to addition of antipsychotic to SRI, and then discontinued antipsychotic.

- Follow-up = 1 year.

- 15 patients (83.3%) ‘relapsed’ after antipsychotic discontinuation, with a mean worsening of Y-BOCS of 6.6 +/- 1.7 points

- 13 patients relapsed by week 8 after discontinuation. Two subjects relapsed at the end of the 1-year follow-up.

- Conclusions: Initial evidence that antipsychotic may need to be maintained for patients who respond to this strategy because the majority who discontinue antipsychotic relapse within 2 months.
Does adding CBT to SRI protect against relapse after drug discontinuation?
No properly controlled, blinded studies

**Biondi et al (2005)**
- 10/20 SRI-responders non-randomly allocated CBT timed to end after SRI openly discontinued
- Time to relapse sig longer for CBT+SRI ($p<0.001$)

**Simpson et al (2005)**
- Post-hoc survival analysis of acute-phase responders
- CMI ($N=13$), CMI+ERP ($N=15$), ERP ($N=18$) placebo ($N=2$)
- Following open discontinuation (wk12-24):
  - [ERP and CMI+ERP] > CMI on proportion and time to relapse on some but not all relapse criteria
Defining OCD - ICD-10

A. Either obsessions or compulsions (or both) [present on most days for a period of at least two weeks]

B. Obsessions (thoughts, images or ideas) and compulsions share the following features, all of which must be present:

- Acknowledged as originating in the mind of the individual
- Repetitive and unpleasant; at least one recognised as excessive or unreasonable
- At least one must be unsuccessfully resisted (although resistance may be minimal in some cases)
- Carrying out the obsessive thought or compulsive act is not intrinsically pleasurable
The obsessive compulsive spectrum

Hollander et al. CNS Spectrums 2007;12:5–13