Obsessive compulsive disorder

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QUESTIONS

INTERVENTIONS

OCD TREATMENTS IN ADULTS

Beneficial

Unknown effectiveness

BEST MAINTENANCE FOR OCD

Unknown effectiveness

TREATMENT: NON-RESPONDERS TO SRIS

Likely to be beneficial

To be covered in future updates

Deep brain stimulation

Other adjuvant/augmentation drug treatment

Other drug monotherapies

Other forms of psychotherapy

Psychosurgery

Transcranial magnetic stimulation

Key Points

- Obsessions or compulsions that cause personal distress or social dysfunction affect about 1% of men and 2% of women.

  About half of people with obsessive compulsive disorder (OCD) have an episodic course, whereas the other half have continuous problems. Up to half of people show improvement of symptoms over time.

- Cognitive behavioural therapy improves symptoms of OCD compared with a waiting list control.

  Behavioural therapy seems to be as effective at improving symptoms as cognitive behavioural therapy, but we do not know how it compares with serotonin reuptake inhibitors. Behavioural therapy is more effective than relaxation.

  We do not know whether combining serotonin reuptake inhibitors and cognitive therapy or behavioural therapy improves symptoms compared with each treatment alone.

- Selective and non-selective serotonin reuptake inhibitors improve symptoms of OCD compared with placebo, but increase the risk of adverse effects.

  Selective and non-selective serotonin reuptake inhibitors seem to be more effective at reducing symptoms compared with tricyclic antidepressants or monoamine oxidase inhibitors.

  Venlafaxine may be as effective as SSRIs, but sertraline has not been consistently shown to be beneficial.

  We do not know which is the most effective drug to use, or for how long maintenance treatment should continue.

- CAUTION: SSRIs have been associated with an increase in suicidal ideation.

- Adding antipsychotic drugs to SSRIs may improve symptoms in people who did not respond to SSRIs, although studies have given conflicting results.

- We do not know whether electroconvulsive therapy improves symptoms in people with OCD.

DEFINITION

Obsessive compulsive disorder (OCD) involves obsessions, compulsions, or both, that are not caused by drugs or by a physical disorder, and which cause significant personal distress or social dysfunction. [1] [2] The disorder may have a chronic or an episodic course. **Obsessions** are recurrent and persistent ideas, images, or impulses that cause pronounced anxiety and that the person perceives to be self produced. **Compulsions** are repetitive behaviours or mental acts performed in response to obsessions or according to certain rules, which are aimed at reducing distress or preventing certain imagined dreaded events. People with OCD may have insight into their condition, in that obsessions and compulsions are usually recognised and resisted. There are minor differences in the criteria for OCD between the third, revised third, and fourth editions of the *Diagnostic and Statistical Manual* (DSM-III, DSM-III-R, and DSM-IV) [1] and *The ICD-10 Classification of Mental and Behavioural Disorders*. [2]

INCIDENCE/ PREVALENCE

One national, community based survey of OCD in the UK (1993, 10 000 people) found that 1.0% of men and 1.5% of women reported symptoms in the previous month. [3] A survey of a random sample of people living in private households in the UK (2000, 8580 adults aged 16–74 years) found that 1.1% of those surveyed reported symptoms of OCD during the previous week. [4] An epidemiological catchment area survey carried out in the USA in 1984 (about 10 000 people) found an age and sex standardised annual prevalence of OCD in people aged 26–64 years of 1.3%, and a lifetime prevalence of 2.3%. [5] Subsequent national surveys used a similar methodology to the survey in the USA, and found broadly similar age and sex standardised annual and lifetime prevalence rates in Canada, Puerto Rico, Germany, Korea, and New Zealand, but a slightly lower prevalence in Taiwan (see table 1, p 00, p 14). [5]

AETIOLOGY/ RISK FACTORS

The cause of OCD is uncertain. Behavioural, cognitive, genetic, and neurobiological factors have been implicated. [6] [7] [8] [9] [10] [11] [12] Limited evidence from genetic studies in families, and in twins, suggests that genetic factors may be involved, at least in some groups. [8] [13] [14] [15] [16] [17] Risk factors include a family history of OCD, being single (which could be a consequence of the disorder), and belonging to a higher socioeconomic class. [18] The risk of OCD in women is higher than in men in most countries. [5] Other risk factors include cocaine abuse, not being in paid employment, past history of alcohol dependence, affective disorder, and phobic disorder. [5]

PROGNOSIS

One study (144 people followed for a mean of 47 years) found that an episodic course of OCD was more common during the initial years (about 1–9 years), but that a chronic course was more common afterwards. [19] Over time, the study found that 39–48% of people had symptomatic improvement. A 1 year prospective cohort study found that 46% of people had an episodic course and 54% had a chronic course. [20]

AIMS OF INTERVENTION

To improve symptoms, and to reduce the impact of illness on social functioning and quality of life, with minimal adverse effects of treatment.

OUTCOMES

Severity of symptoms; social functioning; and adverse effects of treatment. Commonly used instruments for measuring symptoms include the Hamilton Anxiety Rating Scale ; the Hamilton Depression Rating Scale ; and the Yale–Brown Obsessive Compulsive Scale .

METHODS

BMJ Clinical Evidence search and appraisal July 2006. The following databases were used to identify studies for this review: Medline 1966 to July 2006, Embase 1980 to July 2006, PsycInfo 1967 to July 2006, and The Cochrane Database of Systematic Reviews 2006, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) – for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE) clinical guidelines. Abstracts of the studies retrieved were assessed independently by two information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 people, of whom more than 80% were followed up. There was no minimum length of follow up required to evaluate studies. We excluded all studies described as “open”, “open label“, or not blinded, unless the interventions could not be blinded. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required.

QUESTION What are the effects of initial treatments for obsessive compulsive disorder in adults?

OPTION BEHAVIOURAL THERAPY

We found no RCTs comparing behavioural therapy versus no treatment. One systematic review and one subsequent RCT found that behavioural therapy improved symptoms compared with relaxation. The review and four subsequent RCTs found no consistent evidence of a difference in symptoms between behavioural therapy and cognitive therapy or cognitive behavioural therapy. One small RCT found that behavioural therapy plus relaxation improved symptoms at 6 weeks compared with waiting list control. It found no significant difference between behavioural therapy plus relaxation and behavioural therapy plus cognitive therapy either at the end of 6 weeks' treatment or at 12 month follow up. One systematic review provided insufficient evidence from indirect comparisons to compare serotonin reuptake inhibitors versus behavioural therapy. RCTs provided insufficient evidence to assess the effects of adding serotonin reuptake inhibitors to behavioural or cognitive therapy.

Benefits:

Behavioural therapy versus no treatment:
We found no systematic review or RCTs.

Behavioural therapy versus relaxation:
We found one systematic review (search date 1995, 2 RCTs, 121 people), which found that behavioural therapy significantly improved symptoms over 4–16 weeks of treatment compared with relaxation (standardised mean differences 1.18, CI not reported; P < 0.01). [21] One subsequent RCT (218 people with *Diagnostic and Statistical Manual* [DSM]-IV with obsessive compulsive disorder [OCD], 49% of whom were also taking a serotonin reuptake inhibitor) compared three treatments: behavioural therapy guided by a computer, behavioural therapy guided by a clinician, and relaxation. [22] It found that both types of behavioural therapy significantly improved Yale–Brown Obsessive Compulsive Scale (YBOCS) score after 10 weeks of treatment compared with relaxation (mean reduction: 5.6 with computer guided behavioural therapy *v* 8.0 with clinician guided behavioural therapy *v* 1.7 with relaxation; P = 0.001 for relaxation *v* either type of behavioural therapy; P = 0.035 for clinician guided *v* computer guided behavioural therapy; analysis not by intention to treat). [22]

Behavioural therapy versus cognitive therapy or cognitive behavioural therapy:
We found one systematic review [21] and four subsequent RCTs. [23] [24] [25] [26] The systematic review (search date 1995, 4 RCTs, 92 people) found no significant difference in symptoms over 4–16 weeks between behavioural therapy and cognitive therapy (SMD –0.19; reported as P > 0.05, no further data reported). [21] The first subsequent RCT (76 people) found no significant difference between group behavioural therapy (exposure with response prevention) and group cognitive behavioural therapy in recovery (defined as a greater than or equal to 6 point YBOCS score reduction and score less than or equal to 12) immediately after 12 weeks of treatment (AR: 12/32 [38%] with behavioural therapy *v* 5/31 [16%] with cognitive behavioural therapy; P = 0.09). However, it found that behavioural therapy significantly improved recovery at 3 months' follow up compared with cognitive behavioural therapy (AR: 14/31 [45%] with behavioural therapy *v* 4/31 [13%] with cognitive behavioural therapy; P = 0.01; analysis not by intention to treat). [23] The second subsequent RCT (63 people) found no significant difference between behavioural therapy and cognitive therapy in the proportion of people achieving at least 25% improvement in YBOCS score after 16 weeks of treatment (OR 0.7, 95% CI 0.2 to 2.0). [24] The third subsequent RCT compared 12 sessions of behavioural therapy versus 12 individual sessions of cognitive therapy. [25] It found that, after treatment, cognitive therapy significantly improved OCD behaviours (assessed using the Maudsley Obsessional Compulsive Inventory) compared with behavioural therapy but found no significant difference between treatments on the YBOCS score (22 people with DSM-III-R diagnosis of OCD, 18 completed treatment; results presented graphically; P = 0.006 for the Maudsley Inventory; P = 0.022 for YBOCS, not significant after adjusting for multiple outcome measures). [i] The fourth subsequent RCT (54 adults [44 completed] with DSM-IV OCD) compared weekly sessions for 20 weeks of: an inference based approach (16 people); a cognitive appraisal model (16 people); and exposure and response prevention (12 people). [26] The inference based approach consisted of challenging the primary reasoning (inference) about the obsession (e.g. the door knob is contaminated); the cognitive appraisal model (the same as cognitive therapy) used education in normalisation of the primary inference, then subsequently challenged the exaggerated appraisals of such inference; exposure and response prevention consisted of standard exposure and response prevention. The RCT found no significant difference between groups in the YBOCS score (YBOCS score preintervention to postintervention: 19.2 to 10.4 with exposure and response prevention *v* 25.5 to 13.3 with the cognitive appraisal model *v* 25.3 to 13.1 with the inference based approach; between group P value = 0.51). [26] The results were based on 44/54 (81%) people who completed 20 weeks' treatment, and the analysis was not by intention to treat. [26]

Behavioural therapy versus serotonin reuptake inhibitors:
See benefits of serotonin reuptake inhibitors, p 6 .

Behavioural therapy plus serotonin reuptake inhibitors:
See benefits of behavioural therapy or cognitive therapy plus serotonin reuptake inhibitors, p 9 .

Behavioural therapy plus relaxation:
We found one RCT, which compared three treatments: individual behavioural therapy plus cognitive therapy (cognitive behavioural therapy); individual behavioural therapy plus relaxation; and waiting list control. [27] People were initially randomised to the two active treatments or to waiting list control for 6 weeks; after 6 weeks, people on the waiting list were randomly allocated to the two active treatments. Both active treatment groups received relapse prevention follow up. People who were on stable doses of antiobsessional medication continued with medications during the study. The RCT found that behavioural therapy plus relaxation significantly decreased the YBOCS scores at 6 weeks compared with waiting list control (3 arm RCT; 35 people with DSM-III-R diagnosis of OCD, 29 people included in 6 week analysis; YBOCS scores: 10.1 with behavioural therapy plus relaxation *v* 25.2 with waiting list control; P < 0.017). It found no significant difference in symptom scores or the proportion of people improved between behavioural therapy plus relaxation and cognitive behavioural therapy either after treatment or at 12 months' follow up (after treatment results include people who received active treatments after 6 weeks on the waiting list; YBOCS after treatment: 16.7 with cognitive behavioural therapy *v* 16.1 with behavioural therapy plus relaxation; YBOCS at 12 months: 14.8 with cognitive behavioural therapy *v* 15.4 with behavioural therapy plus relaxation; P > 0.017 for both comparisons; improvement defined as YBOCS score < 16, AR for improvement: 6/16 [38%] with cognitive behavioural therapy *v* 10/19 [53%] with behavioural therapy plus relaxation; reported as not significant, P value not reported). In this RCT the level required for significance was P < 0.017 after Bonferroni correction for multiple comparisons. [27]

Harms:

Case reports have described unbearable and unacceptable anxiety in some people receiving behavioural therapy.

Behavioural therapy versus cognitive therapy or cognitive behavioural therapy:
The third subsequent RCT found that three people (3/11 [27%]) withdrew from behavioural therapy and one person (1/10 [10%]) from cognitive therapy. [25] [i] The fourth subsequent RCT did not report on adverse effects. [26]

Behavioural therapy plus relaxation:
The RCT found that seven people (7/19 [37%]) withdrew from behavioural therapy plus relaxation compared with one person (1/16 [6%]) from cognitive behavioural therapy. [27] It found that some people experienced an increase in comorbid symptoms (panic, depression, substance misuse) during treatment and many of these people withdrew (actual numbers and treatment groups not reported). One person receiving cognitive behavioural therapy had a relapse of an alcohol abuse problem but was able to complete the treatment. One person receiving behavioural therapy plus relaxation became increasingly suicidal and was removed from the study.

Comment:

Clinical guide:
Factors predicting outcome: we found two RCTs of behavioural therapy (total 96 people, duration 2.5 months [27] and 32 weeks [28]) and two retrospective cohort studies (total 346 people, duration 1 year [29] and 11 weeks [30]), which assessed factors predicting outcome. These found that poorer outcome was predicted by initial severity, depression, longer duration, poorer motivation, and dissatisfaction with the therapeutic relationship. Good outcome was predicted by early adherence to exposure homework , employment, living with one's family, no previous treatment, having fear of contamination, overt ritualistic behaviour, and absence of depression. [27] [28] [29] Good outcome for women was predicted by having a co-therapist (someone, usually related to the person concerned, who is enlisted to help with treatment outside regular treatment sessions). [31] Two systematic reviews of drug, behavioural, cognitive, and combination treatments for OCD are being prepared. Maintenance of improvement: a prospective follow up (20 people with OCD, specific diagnostic criteria not reported) after a 6 month RCT of behavioural therapy found that 79% maintained improvement in OCD symptoms at 2 years of follow up. [32] A prospective non-inception cohort study of behavioural therapy in 21 people with OCD (specific diagnostic criteria not reported) found that, after 2 weeks of treatment, 68–79% maintained complete or much improvement in symptoms at 3 months of follow up. [33] In both studies, some people received additional behavioural therapy during follow up. We found another RCT which compared cognitive behavioural therapy versus exposure and response prevention. [34] However, it had a high withdrawal rate (30%), and therefore did not meet *BMJ Clinical Evidence* criteria for inclusion (< 20% withdrawal).

OPTION COGNITIVE THERAPY OR COGNITIVE BEHAVIOURAL THERAPY

We found no RCTs comparing cognitive therapy versus no treatment. Two RCTs found that cognitive behavioural therapy improved symptoms compared with no treatment or waiting list control after 6–12 weeks. One systematic review and four subsequent RCTs found no consistent evidence of a difference in symptoms between behavioural therapy and cognitive therapy or cognitive behavioural therapy.

Benefits:

Cognitive therapy or cognitive behavioural therapy versus no treatment:
We found two RCTs. [27] [35] The first RCT (47 people with *Diagnostic and Statistical Manual* [DSM]-IV obsessive compulsive disorder, 45% of whom were also taking a serotonin reuptake inhibitor), which compared group cognitive behavioural therapy versus no therapy. [35] It found that group cognitive behavioural therapy significantly increased the proportion of people achieving at least 35% improvement in Yale–Brown Obsessive Compulsive Scale (YBOCS) score after 12 weeks of treatment, and significantly improved quality of life compared with no treatment (proportion achieving at least 35% improvement: 16/23 [69.6%] with group cognitive behavioural therapy *v* 1/24 [4.2%] with no treatment, OR 16.7, 95% CI 2.2 to 115.9; mean reduction in YBOCS score: 11.6 with group cognitive behavioural therapy *v* 1.5 with no treatment, P value not reported; difference in quality of life measured on World Health Organization Quality of Life Assessment — Abbreviated Version: P < 0.04 in favour of cognitive behavioural therapy). [35] The second RCT compared three treatments: individual cognitive behavioural therapy; individual behavioural therapy plus relaxation; and waiting list control (see benefits of behavioural therapy for details, p 3). [27] The RCT found that cognitive behavioural therapy significantly decreased the YBOCS scores at 6 weeks compared with waiting list control (3 arm RCT; 35 people with DSM-III-R diagnosis of OCD, 29 people included in 6 week analysis; YBOCS scores: 13.6 with cognitive behavioural therapy *v* 25.2 with waiting list control; P < 0.017). In this RCT the level required for significance was calculated as P < 0.017 using a Bonferroni correction for multiple comparisons. [27]

Cognitive therapy or cognitive behavioural therapy versus behavioural therapy:
See benefits of behavioural therapy, p 3 .

Cognitive therapy or cognitive behavioural therapy plus serotonin reuptake inhibitors:
See benefits of behavioural therapy or cognitive therapy plus serotonin reuptake inhibitors, p 9 .

Harms:

Cognitive therapy or cognitive behavioural therapy versus no treatment:
The first RCT reported that one person withdrew from the treatment group owing to severe anxiety during response prevention and exposure homework exercises. [35] The second RCT found that one person (1/16 [6%]) withdrew from cognitive behavioural therapy. [27] It found that some people experienced an increase in comorbid symptoms (panic, depression, substance misuse) during treatment, and many of these people withdrew (actual numbers and treatment group not reported). One person receiving cognitive behavioural therapy had a relapse of an alcohol abuse problem but was able to complete the treatment.

Cognitive therapy or cognitive behavioural therapy versus behavioural therapy:
See harms of behavioural therapy, p 4 .

Cognitive therapy or cognitive behavioural therapy plus serotonin reuptake inhibitors:
See harms of behavioural therapy or cognitive therapy plus serotonin reuptake inhibitors, p 9 .

Comment:

We found another RCT, which compared four treatments: intensive individual cognitive behavioural therapy plus clomipramine; intensive individual cognitive behavioural therapy alone; clomipramine alone; and pill placebo. [36] However, it had a high withdrawal rate (42%), and therefore did not meet *BMJ Clinical Evidence* criteria for inclusion (< 20% withdrawal).

Clinical guide:
Cognitive, behavioural, and cognitive behavioural therapies are all effective in obsessive compulsive disorder. However, some people may find it difficult to engage in or complete these interventions because of excessive anxiety during the exposure. In such people it may be appropriate to use SSRIs.

OPTION SEROTONIN REUPTAKE INHIBITORS (CITALOPRAM, CLOMIPRAMINE, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE)

RCTs found that selective and non-selective serotonin reuptake inhibitors (citalopram, clomipramine, fluoxetine, fluvoxamine, paroxetine) improved symptoms compared with placebo, but increased adverse effects. Two systematic reviews found inconsistent results concerning the effects of sertraline compared with

placebo. RCTs have found that selective and non-selective serotonin reuptake inhibitors (clomipramine, fluoxetine, sertraline) improve symptoms compared with tricyclic antidepressants or monoamine oxidase inhibitors. RCTs found no consistent evidence of a difference in efficacy among serotonin reuptake inhibitors, but found that the non-selective serotonin reuptake inhibitor clomipramine was associated with more adverse effects than were selective serotonin reuptake inhibitors. One RCT found no significant difference in symptoms between clomipramine and venlafaxine, but it is likely to have been underpowered to detect a clinically important difference. One RCT found no significant difference in symptoms between venlafaxine and paroxetine. One systematic review provided insufficient evidence from indirect comparisons to compare serotonin reuptake inhibitors versus behavioural therapy. RCTs provided insufficient evidence to assess the effects of adding serotonin reuptake inhibitors to behavioural therapy or cognitive therapy. Selective serotonin reuptake inhibitors have been linked to suicidal ideation. Abrupt withdrawal of selective serotonin reuptake inhibitors should be avoided.

Benefits:

Serotonin reuptake inhibitors versus placebo:
We found two systematic reviews (search dates 1994 [37] and not reported [38]) and five subsequent RCTs (see comment below). [39] [40] [41] [42] [43] The two systematic reviews and subsequent RCTs found that the selective or non-selective serotonin reuptake inhibitors citalopram, clomipramine, fluoxetine, fluvoxamine, and paroxetine (40–60 mg/day) significantly improved symptoms compared with placebo (see comment below). [37] [38] [39] [40] [41] [42] [43] One of the subsequent RCTs found no significant difference in symptoms between paroxetine 20 mg daily and placebo. [39] The two reviews found differing results for sertraline compared with placebo (see comments). [37] [38] The first review found that sertraline significantly improved symptoms compared with placebo, [37] but the second review found no significant difference in symptoms between sertraline and placebo (see table 2, p 15). [38] This may have been due to different methods of meta-analysis (see comment below).

Serotonin reuptake inhibitors versus each other:
We found two systematic reviews (search date 1994; [37] search date not reported [38]) and five subsequent RCTs. [44] [45] [46] [47] [48] The systematic reviews [37] [38] and four of the subsequent RCTs [45] [46] [47] [48] all found no significant difference in symptoms between different selective and non-selective serotonin reuptake inhibitors (see table 3, p 16). However, the first subsequent RCT found that sertraline significantly improved symptoms compared with clomipramine (see table 3, p 16). [44] In this RCT, people taking clomipramine received low doses (median 90 mg/day). This makes the results of the RCT difficult to interpret.

Serotonin reuptake inhibitors versus tricyclic antidepressants and monoamine oxidase inhibitors:
We found one systematic review [37] and two subsequent RCTs. [49] [50] These found that serotonin reuptake inhibitors significantly improved symptoms compared with tricyclic antidepressants or monoamine oxidase inhibitors. The systematic review (search date 1994, 7 RCTs, 147 people with OCD, including 67 children/adolescents) found that, compared with tricyclic antidepressants (desipramine, imipramine, nortriptyline) or monoamine oxidase inhibitors (clorgiline, phenelzine), clomipramine significantly improved symptoms (SMD 0.65, 95% CI 0.36 to 0.92). [37] The first subsequent RCT (54 people) compared three interventions: fluoxetine, phenelzine (a monoamine oxidase inhibitor), and placebo. [49] It found that fluoxetine significantly improved symptoms over 10 weeks compared with phenelzine or placebo (mean reduction in Yale–Brown Obsessive Compulsive Scale (YBOCS) score: 2.8 with fluoxetine *v* 1.7 with phenelzine *v* 0.2 with placebo; P < 0.05 for fluoxetine *v* either comparator). The second subsequent RCT (164 people with concurrent OCD and major depressive disorder) found that sertraline significantly increased the proportion of people who had a clinically important reduction in OCD symptoms compared with desipramine (> 40% improvement on YBOCS: 38/79 [48%] with sertraline *v* 26/85 [31%] with desipramine; P = 0.01) and significantly increased the proportion of people with remission of depressive symptoms (< 7 on Hamilton Depression Rating Scale : 39/79 [49%] with sertraline *v* 30/85 [35%] with desipramine; P = 0.04). [50]

Serotonin reuptake inhibitors versus venlafaxine:
We found two RCTs. [51] [52] The first RCT (73 people) compared clomipramine (150–225 mg/day, 47 people) versus venlafaxine (225–350 mg/day, 26 people). [51] It found no significant difference in response at 12 weeks between clomipramine and venlafaxine (response was defined as greater than or equal to 35% reduction in the YBOCS score and a Clinical Global Impression Scale score of greater than or equal to 2: 9/25 [36%] with venlafaxine *v* 20/40 [50%] with clomipramine; RR 1.39, 95% CI 0.76 to 2.55). [51] The second RCT (150 people) compared paroxetine 60 mg daily versus venlafaxine 300 mg daily for 12 weeks. [52] It found no significant difference between groups in reduction in the YBOCS score or anxiety after 12 weeks (mean reduction in YBOCS score: 7.8 with paroxetine *v* 7.2 with venlafaxine, P = 0.797; reduction in anxiety, measured using the Hamilton Anxiety Rating Scale : 4.7 with paroxetine *v* 4.9 with venlafaxine, P = 0.237). [52]

Serotonin reuptake inhibitors versus behavioural therapy:
We found one systematic review (search date 1997, number of studies and people not reported) which included a meta-analysis. [53] It found no significant difference in symptoms among serotonin reuptake inhibitors, behavioural therapy , and placebo. [53] However, we were unable to draw reliable conclusions as the review made indirect comparisons of effect sizes, and included data from non-randomised studies (see benefits of behavioural or cognitive therapy plus serotonin reuptake inhibitors, p 9).

Serotonin reuptake inhibitors plus behavioural therapy or cognitive therapy:
See behavioural therapy or cognitive therapy plus serotonin reuptake inhibitors, p 9 .

Harms:

Serotonin reuptake inhibitors versus placebo:
One systematic review (search date 1995, 16 RCTs) found that serotonin reuptake inhibitors significantly increased overall adverse effects (unspecified) compared with placebo (RRI *v* placebo: 54% with clomipramine, 11% with fluoxetine, 19% with fluvoxamine, 27% with sertraline). [21] The other systematic reviews gave no information on adverse effects. [37] [38] The first subsequent RCT found that fluoxetine significantly increased tremor ($P < 0.001$), dry mouth ($P < 0.001$), and nausea ($P < 0.01$) compared with placebo (absolute numbers presented graphically). [40] The second subsequent RCT found that citalopram significantly increased nausea, insomnia, fatigue, sweating, dry mouth, and ejaculatory failure compared with placebo ($P < 0.05$). [41] The third subsequent RCT (253 people) found that more people withdrew because of adverse effects with controlled release fluvoxamine than with placebo (20% with fluvoxamine *v* 7% with placebo; P value not reported). [42] Compared with placebo, fluvoxamine increased insomnia (35% with fluvoxamine *v* 20% with placebo), somnolence (27% with fluvoxamine *v* 11% with placebo), asthenia (25% with fluvoxamine *v* 8% with placebo), nausea (34% with fluvoxamine *v* 13% with placebo), diarrhoea (18% with fluvoxamine *v* 8% with placebo), and anorexia (13% with fluvoxamine *v* 5% with placebo), and decreased libido (7% with fluvoxamine *v* 3% with placebo). The fourth subsequent RCT found that the most common adverse effects experienced with paroxetine (60, 40, or 20 mg) compared with placebo at 12 weeks were: abnormal ejaculation (30% with 60 mg *v* 32% with 40 mg *v* 19% with 20 mg *v* 2% with placebo), insomnia (27% with 60 mg *v* 27% with 40 mg *v* 15% with 20 mg *v* 12% with placebo), nausea (18% with 60 mg *v* 26% with 40 mg *v* 20% with 20 mg *v* 8% with placebo), and somnolence (33% with 60 mg *v* 23% with 40 mg *v* 25% with 20 mg *v* 10% with placebo; P values not reported). [43] Headache was less common with paroxetine than with placebo (24% with 60 mg paroxetine *v* 28% with 40 mg paroxetine *v* 19% with 20 mg paroxetine *v* 33% with placebo; P value not reported). The fifth subsequent RCT (191 Japanese people) found that paroxetine significantly increased nausea (28/95 [30%] with paroxetine *v* 7/94 [7%] with placebo), constipation (13/95 [14%] with paroxetine *v* 3/94 [3%] with placebo), and insomnia (8/95 [8%] with paroxetine *v* 0/94 [0%] with placebo), and decreased appetite (10/95 [11%] with paroxetine *v* 2/94 [2%] with placebo; $P < 0.05$ for all comparisons) at 12 weeks compared with placebo. [43]

Serotonin reuptake inhibitors versus each other:
The systematic reviews gave no information on adverse effects. [37] [38] Three subsequent RCTs found that clomipramine increased adverse effects compared with selective serotonin reuptake inhibitors, [44] [45] [46] and one subsequent RCT [47] found no significant difference in adverse effects between the selective serotonin reuptake inhibitors sertraline and fluoxetine. The first subsequent RCT (170 people) found that significantly more people withdrew because of adverse effects with clomipramine than with sertraline ($P < 0.05$). [44] Clomipramine was associated with dry mouth, nausea, tremor, anxiety, and constipation, whereas sertraline was associated with nausea and diarrhoea. The second subsequent RCT (133 people) found that clomipramine significantly increased dry mouth (38% with clomipramine *v* 10% with fluvoxamine) and constipation (26% with clomipramine *v* 10% with fluvoxamine) compared with fluvoxamine ($P < 0.05$). [45] The third subsequent RCT comparing clomipramine versus fluvoxamine (227 people) found that more people stopped clomipramine prematurely (withdrawal: 16% with clomipramine *v* 8% with fluvoxamine; CI not reported), and found that clomipramine significantly increased the proportion of people who had anticholinergic adverse effects (dry mouth: 43% with clomipramine *v* 10% with fluvoxamine; constipation: 25% with clomipramine *v* 9% with fluvoxamine; tremor: 22% with clomipramine *v* 9% with fluvoxamine; and dizziness: 18% with clomipramine *v* 7% with fluvoxamine; $P = 0.05$ for frequency of all anticholinergic adverse effects with clomipramine *v* fluvoxamine). [46] The fourth subsequent RCT found no significant difference in adverse effects between sertraline and fluoxetine. [47] The fifth subsequent RCT gave no information on adverse effects. [48] One systematic review (search date 1997) of controlled and uncontrolled studies found that the withdrawal rate from adverse effects was 11% with clomipramine, 10% with fluoxetine, 13% with fluvoxamine, 9% with sertraline, and 11% with paroxetine. [53] One non-systematic review of three prospective cohort studies and five surveys found that fluoxetine during pregnancy did not increase the risk of spontaneous abortion or major malformation (numerical values not reported). [54] The review included one prospective cohort study (174 people), and three surveys that found similar outcomes with other selective serotonin reuptake inhibitors (sertraline, paroxetine, and fluvoxamine). One prospective cohort

study of 55 preschool children exposed to fluoxetine *in utero* found no significant difference from unexposed children in global intelligence quotient, language, or behaviour. It included no information on long term harms for the other selective serotonin reuptake inhibitors. The non-systematic review of effects in pregnancy did not describe how articles were selected. [54]

Serotonin reuptake inhibitors versus tricyclic antidepressants and monoamine oxidase inhibitors:
The systematic review gave no information on adverse effects. [37] The second subsequent RCT (164 people) found that significantly more people discontinued treatment because of adverse effects with desipramine than with sertraline (26% with desipramine *v* 10% with sertraline; P = 0.009). [50] One systematic review comparing the harms of selective serotonin reuptake inhibitors versus tricyclic antidepressants found that selective serotonin reuptake inhibitors were associated with fewer anticholinergic adverse effects, but more nausea, diarrhoea, anxiety, agitation, insomnia, and headache. [55]

Serotonin reuptake inhibitors versus venlafaxine:
The first RCT (73 people) found that significantly more people had overall adverse effects with clomipramine than with venlafaxine (43/47 [92%] with clomipramine *v* 16/26 [62%] with venlafaxine; P = 0.002). [51] It found that, compared with venlafaxine, clomipramine significantly increased the proportion of people who had dry mouth (16/47 [34%] with clomipramine *v* 3/26 [12%] with venlafaxine; P = 0.036) and constipation (17/47 [36%] with clomipramine *v* 2/26 [8%] with venlafaxine; P = 0.008). The second RCT (150 people) found that the most common adverse effects included somnolence (41% with paroxetine *v* 44% with venlafaxine), sweating (28% with paroxetine *v* 32% with venlafaxine), constipation (11% with paroxetine *v* 23% with venlafaxine), insomnia (17% with paroxetine *v* 39% with venlafaxine), and nausea (27% with paroxetine *v* 27% with venlafaxine; significance not stated and P values not reported). [52]

[i] Drug alert:
SSRIs have been linked to suicidal ideation. In clinical trials in children and adolescents with depression, SSRIs have been reported to increase rates of suicide related events. [56] [57] Extrapyramidal reactions (including orofacial dystonias) and withdrawal syndrome have been reported more commonly with paroxetine than with other SSRIs. [58] Other alerts and revised prescribing information regarding the use of SSRIs include the increased risk of persistent pulmonary hypertension in infants born to women who had taken SSRIs during the later half of pregnancy; the increased risk of congenital malformations in infants born to women taking paroxetine during first trimester of pregnancy, and the potential for SSRIs to cause hyponatraemia, particularly in elderly. [59] [60] [61] See also harms of SSRIs in depression in adults and depression in children and adolescents.

Comment:

Clinical guide:
Abrupt withdrawal or marked reduction in the dose of SSRIs should be avoided as it can be associated with adverse effects such as gastrointestinal disturbances, headache, anxiety, dizziness, paraesthesia, sleep disturbances, fatigue, influenza-like symptoms, and sweating. [58] The dose should be tapered over a few weeks to avoid these effects. See also harms of SSRIs in depression in adults and depression in children and adolescents.

Serotonin reuptake inhibitors versus placebo:
One of the reviews found that sertraline was more effective than placebo, [37] whereas the other did not. [38] This may have been because of different methods of meta-analysis. The reviews found heterogeneity in the selection of participants and duration of treatment in the RCTs identified; the first review [37] found that this heterogeneity reached significance in RCTs comparing clomipramine versus placebo. Two RCTs comparing clomipramine versus placebo in the first review included 73 children, but the review did not analyse these RCTs separately. [37] Some RCTs identified by the reviews included people with depression associated with OCD. The first systematic review performed a subgroup analysis in people with OCD without depression and found that, compared with placebo, clomipramine improved symptoms of OCD in people without depression (5 RCTs, 594 people, standardised mean differences 1.37, 95% CI 1.19 to 1.55). [37] This suggests that the effect of serotonin reuptake inhibitors on OCD symptoms is independent of their effect on symptoms of depression. We found another RCT (149 people, randomised) that compared four treatments over 12 weeks: intensive individual cognitive behavioural therapy plus clomipramine, intensive individual cognitive behavioural therapy alone, clomipramine alone, and pill placebo. [36] However, the RCT had a high withdrawal rate (62/149 [42%]) and therefore did not meet *BMJ Clinical Evidence* inclusion criteria (< 20% withdrawal). [36]

Factors predicting outcome:
Four RCTs found that people who did not respond to serotonin reuptake inhibitors had a younger age of onset, longer duration of the condition, higher frequency of symptoms, coexisting personality disorders, and a greater likelihood of previous hospital admission. Predictors of good response

were older age of onset, history of remissions, no previous drug treatment, more severe OCD, and either high or low score on the Hamilton Depression Rating Scale . [62] [63] [64] [65] Two cohort studies of people with OCD found that poor response to serotonin reuptake inhibitors was predicted by concomitant schizotypal personality disorder , tic disorder , and also severe OCD with cleaning rituals (OR 4.9, 95% CI 1.1 to 21.2). [66] [67]

OPTION BEHAVIOURAL THERAPY OR COGNITIVE THERAPY PLUS SEROTONIN REUPTAKE INHIBITORS

One systematic review and three subsequent RCTs provided insufficient evidence to assess the effects of adding serotonin reuptake inhibitors to behavioural therapy or cognitive therapy.

Benefits: We found one systematic review [53] and three subsequent RCTs. [68] [69] [70] The systematic review (search date 1997, 77 studies, number of people not reported, relative number of RCTs or other study types not reported, 70% of treatment comparisons randomised) did not make direct comparisons between treatments. [53] It included all types of study, with the exception of case control studies, and did not describe individual studies included in each analysis. In indirect comparisons, it found similar reductions in symptoms with behavioural therapy alone versus placebo, behavioural therapy plus serotonin reuptake inhibitors (clomipramine, fluoxetine, fluvoxamine, paroxetine, or sertraline) versus placebo, and serotonin reuptake inhibitors alone versus placebo. However, we were unable to draw reliable conclusions as the review made indirect comparisons of effect sizes, and included data from non-randomised studies. The first subsequent RCT (99 people in an outpatient setting) compared four interventions: behavioural therapy, cognitive therapy , behavioural therapy plus fluvoxamine (a selective serotonin reuptake inhibitor), and cognitive therapy plus fluvoxamine. It found no significant difference among interventions in symptoms after 16 weeks of treatment (mean reduction in Yale–Brown Obsessive Compulsive Scale [YBOCS] score: 17.1 with behavioural therapy *v* 13.5 with cognitive therapy *v* 12.6 with behavioural therapy plus fluvoxamine *v* 15.6 with cognitive therapy plus fluvoxamine, reported as not significant, no further data reported). [68] The second subsequent RCT (49 people in a hospital setting) found that behavioural therapy plus fluvoxamine significantly increased the proportion of people with improved symptoms after 9 weeks of treatment compared with behavioural therapy plus pill placebo (number of people with > 35% reduction in the YBOCS score: 21/24 [88%] with behavioural therapy plus fluvoxamine *v* 15/25 [60%] with behavioural therapy plus pill placebo; RR 1.46, 95% CI 1.02 to 2.08). [69] [i] The third subsequent RCT (96 people with *Diagnostic and Statistical Manual* [DSM]-IV OCD who had responded to paroxetine or venlafaxine [shown at least a 25% reduction in YBOCS in a previous RCT comparing paroxetine versus venlafaxine]) compared current drug treatment versus current drug treatment plus behaviour therapy (combination treatment) for a duration of 6 months. [70] Behavioural therapy consisted of exposure and response prevention and was given as 18 sessions of 45 minutes. The RCT found that combination treatment significantly reduced the YBOCS score compared with current drug treatment alone (mean YBOCS score preintervention [0 weeks] to postintervention [27 weeks]: 14.47 to 10.56 with combination treatment *v* 14.50 to 18.36 with current drug treatment alone; P < 0.001). [70] However, it found no significant difference between the groups on the Hamilton scale for anxiety (P = 0.48) or the Hamilton scale for depression (P = 0.091). These results were based on 80/96 (83%) of people who completed treatment.

Harms: [i] The systematic review [53] and two subsequent RCTs [69] [70] gave no information on adverse effects. The other subsequent RCT reported more somnolence with fluvoxamine (baseline analysis: pretreatment to 8 weeks: 0% to 17%, P < 0.01, further details, including between group analysis, not reported) and sweating (baseline analysis: pretreatment to 16 weeks: 0% to 22%, P = 0.03, further details, including between group analysis, not reported). [68] We found no evidence from RCTs or cohort studies of adverse effects from behavioural therapy. Case reports have described unbearable and unacceptable anxiety in some people receiving behavioural therapy. See harms of serotonin reuptake inhibitors, p 7 and harms of cognitive or cognitive behavioural therapy, p 5 .

Comment: We found another RCT which compared four treatments: intensive individual cognitive behavioural therapy plus clomipramine, intensive individual cognitive behavioural therapy alone, clomipramine alone, and pill placebo. [36] However, it had a high withdrawal rate (42%) and therefore did not meet *BMJ Clinical Evidence* criteria for inclusion (< 20% withdrawal).

OPTION ELECTROCONVULSIVE THERAPY

We found no RCTs of electroconvulsive therapy in people with obsessive compulsive disorder.

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: People with obsessive compulsive disorder who also have depression may be treated with electroconvulsive therapy. The evidence for the effects of electroconvulsive therapy in depression is summarised elsewhere in *BMJ Clinical Evidence* (see depression in adults).

QUESTION What are the best forms of maintenance treatment for obsessive compulsive disorder in adults?

OPTION OPTIMUM DURATION OF MAINTENANCE TREATMENT WITH SEROTONIN REUPTAKE INHIBITORS

RCTs provided insufficient evidence to define the optimum duration of maintenance treatment with serotonin reuptake inhibitors.

Benefits: We found three RCTs, which assessed maintenance of serotonin reuptake inhibitors in people who had responded to treatment. [39] [71] [72] The first RCT (70 people who had responded to a 20 week course of fluoxetine) found no significant difference between maintenance of fluoxetine and replacement by placebo for 1 year in relapse rate over 1 year (21% with fluoxetine *v* 32% with placebo; P = 0.137). [71] The second RCT compared sertraline versus placebo in 223 people with obsessive compulsive disorder (OCD), who had all previously responded to 1 year's treatment with sertraline (response defined as at least 25% reduction in Yale–Brown Obsessive Compulsive Scale score from baseline). [72] People continuing on sertraline were prescribed their previous dose (mean 183 mg). The RCT found that, compared with placebo, sertraline significantly reduced the proportion of people who withdrew because of relapse or insufficient clinical response over 24 weeks (9% with sertraline *v* 24% with placebo; P = 0.006). It found that sertraline reduced the proportion of people who had worsening of symptoms compared with placebo (12% with sertraline *v* 35% with placebo; P = 0.001). It found no significant difference in relapse rate over 24 weeks (2.7% with sertraline *v* 4.4% with placebo; P = 0.34). [72] The third RCT compared continued paroxetine versus placebo in 105 people with OCD, who had all previously taken part in an 12 week trial of paroxetine (20, 40, or 60 mg/day) versus placebo, and who had all responded to a further 6 months' treatment with paroxetine (flexible dose starting at 20 mg/day to a maximum of 60 mg/day). [43] People randomised to paroxetine continued on the same dose as that taken during the previous 6 months, and those allocated placebo were switched to it immediately. The RCT found that, compared with placebo, paroxetine significantly reduced the risk of relapse compared with placebo over 6 months (20/53 [37.7%] with paroxetine *v* 30/51 [58.8%] with placebo; P less than or equal to 0.033). [43]

Harms: The first RCT found no significant difference between fluoxetine and placebo in overall adverse effects (reported as not significant, adverse effects not specified, absolute numbers and CI not reported) or in the proportion of people who withdrew from the trial for any cause over 52 weeks (16/36 [44%] with fluoxetine *v* 23/35 [66%] with placebo; P = 0.072). [71] The second RCT found that upper respiratory infection, headache, and malaise were reported in 10% or more of people taking sertraline (the RCT did not report rates of these adverse effects with placebo) and that people taking placebo had dizziness and depression (no further data reported). [72] It found that fewer people taking sertraline withdrew because of adverse effects compared with people taking placebo (5/109 [5%] with sertraline *v* 12/114 [11%] with placebo; P value not reported). The third RCT found that three people (6%) withdrew from paroxetine treatment compared with 20 people (39%) from placebo. [43] The most common adverse effects were dizziness (5/53 [9%] with paroxetine *v* 18/52 [35%] with placebo), nausea (5/53 [9%] with paroxetine *v* 14/52 [27%] with placebo), insomnia (4/53 [8%] with paroxetine *v* 14/52 [27%] with placebo), and an increase in OCD symptoms (neurosis: 7/53 [13%] with paroxetine *v* 17/52 [33%] with placebo; see comment). [43] Abrupt substitution of paroxetine with placebo may have contributed to adverse effects in the RCT. [43]

Comment: **Clinical guide:**
Most RCTs of treatments for OCD are conducted for about 8–12 weeks. [73] Trials of this length do not provide evidence about the optimum duration of maintenance and preventive treatment for the condition. Longer RCTs with placebo substitution are required to determine this. A few such trials have been conducted recently, the results of which are summarised in the benefits section above. One prospective, 1 year study found further improvement after a 40 week open label extension of the study, with continuing adverse effects. [74] One observational study found that 16/18 (89%) of people relapsed within 7 weeks of replacing clomipramine with placebo treatment. [75]

QUESTION **What are the effects of treatments for obsessive compulsive disorder in adults who have not responded to initial treatment with serotonin reuptake inhibitors?**

OPTION ADDITION OF ANTIPSYCHOTICS TO SEROTONIN REUPTAKE INHIBITORS

Four small RCTs in people unresponsive to serotonin reuptake inhibitors found that the addition of antipsychotics improved symptoms compared with serotonin reuptake inhibitors plus placebo. However, a fifth small RCT found no significant difference between fluoxetine plus olanzapine compared with fluoxetine plus placebo after 6 weeks.

Benefits:

We found five small RCTs which assessed combined antipsychotics and serotonin reuptake inhibitors in people who did not respond to serotonin reuptake inhibitors alone. [76] [77] [78] [79] [80] The first RCT (34 people with obsessive compulsive disorder who had not responded to 8 weeks of treatment with fluvoxamine) compared fluvoxamine plus haloperidol (maximum dose: 10 mg/day) versus fluvoxamine plus placebo. [76] Response to treatment was assessed using three criteria: a 35% or more reduction in the Yale–Brown Obsessive Compulsive Scale (YBOCS) score with a final YBOCS score of less than 16; a final Clinical Global Impression Scale score of "much improved" or "better", and consensus between the clinician and two of the investigators that the participant's condition had improved. It found that fluvoxamine plus haloperidol significantly increased the proportion of people who met two out of the three different response criteria compared with fluvoxamine plus placebo (11/17 [65%] with fluvoxamine plus haloperidol *v* 0/17 [0%] with fluvoxamine plus placebo; NNT 2, 95% CI 2 to 3; P < 0.0002). The second and third small RCTs compared a serotonin reuptake inhibitor plus risperidone versus serotonin reuptake inhibitor alone. [77] [78] The second RCT (36 people with obsessive compulsive disorder who did not respond to 12 weeks of treatment with a serotonin reuptake inhibitor) found that, compared with the addition of placebo, the addition of 6 weeks of the antipsychotic drug risperidone to the prior serotonin reuptake inhibitor significantly improved symptoms of obsessive compulsive disorder (reduction in the YBOCS score: 36% with risperidone plus serotonin reuptake inhibitor *v* 9% with placebo plus serotonin reuptake inhibitor; P = 0.001), depression (reduction in the Hamilton Depression Rating Scale : 35% with risperidone plus serotonin reuptake inhibitor *v* 20% with placebo plus serotonin reuptake inhibitor; P = 0.002), and anxiety (reduction in the Hamilton Anxiety Rating Scale 31% with risperidone plus serotonin reuptake inhibitor *v* 12% with placebo plus serotonin reuptake inhibitor; P = 0.007). [77] People taking risperidone were more likely to have met two of the response criteria (8/18 [44%] with risperidone plus serotonin reuptake inhibitor *v* 0/15 [0%] with placebo plus serotonin reuptake inhibitor; NNT 2, 95% CI 2 to 3; P < 0.005). The third small RCT (20 people who had not responded to 12 weeks of 150–300 mg/day fluvoxamine, response defined as YBOCS score reduction > 35%) found that adding risperidone 0.5 mg to fluvoxamine increased response rate at 6 weeks compared with risperidone alone, but the significance of this difference was not reported (response: 5/10 [50%] with risperidone plus fluvoxamine *v* 2/10 [20%] with placebo plus fluvoxamine; significance assessment not performed). [78] The fourth and fifth small RCTs compared serotonin reuptake inhibitor plus quetiapine versus serotonin reuptake inhibitor alone. [79] [80] The fourth RCT (27 people who did not respond to 3 months of treatment with fluoxetine, fluvoxamine, or clomipramine in an open label trial) compared a serotonin reuptake inhibitor plus quetiapine (an atypical antipsychotic 50–200 mg/day) versus a serotonin reuptake inhibitor plus placebo for 8 weeks. [79] People received the same serotonin reuptake inhibitors in the RCT as they had in the open label phase of the study. The RCT found that a serotonin reuptake inhibitor plus quetiapine significantly increased the proportion of people who responded compared with a serotonin reuptake inhibitor plus placebo (response defined as greater than or equal to 30% reduction in the YBOCS score: 10/14 [71%] with serotonin reuptake inhibitor plus quetiapine *v* 0/14 [0%] with serotonin reuptake inhibitor plus placebo; P < 0.0001). The fifth RCT (44 people who remained symptomatic and had a moderate Clinical global impression Scale score after 8 weeks of treatment with fluoxetine) compared adding olanzapine (maximum dose of olanzapine 10 mg) versus adding placebo for 6 weeks. [80] It found no significant difference between treatments in reduction in YBOCS score at 6 weeks (5.1 with fluoxetine plus olanzapine *v* 3.8 with fluoxetine plus placebo; reported as non-significant).

Harms:

Extrapyramidal adverse effects are common with haloperidol, which can also cause prolactinaemia. The second RCT found that sedation, restlessness, increased appetite, dry mouth, or tinnitus were experienced by at least 10% of people taking serotonin reuptake inhibitors plus risperidone, and that blurred vision, excessive perspiration, headache, increased appetite, lightheadedness, restlessness, and sedation were experienced by at least 10% of people taking serotonin reuptake inhibitors plus placebo. [77] The third RCT found that fluvoxamine plus risperidone was associated with transient sedation in seven people (7/9 [78%]) and mild appetite increase in three people (3/9 [33%]). [78] The RCT gave no information on adverse effects with fluvoxamine plus placebo. Risperidone is commonly associated with hypotension and hyperprolactinaemia. The fourth RCT of serotonin reuptake inhibitors plus quetiapine found that people taking a serotonin reuptake inhibitor plus quetiapine had nausea (6/14 [43%]), sedation (3/14 [21%]), and dizziness (1/14 [7%]), and

that people taking a serotonin reuptake inhibitor plus placebo had sedation (2/13 [15%]), headache (1/13 [8%]), and nervousness (1/13 [8%]). [78] The sixth RCT, comparing fluoxetine plus olanzapine versus fluoxetine plus placebo, found that five people taking fluoxetine plus olanzapine withdrew from the trial (3 lost to follow up [reasons not stated], 1 withdrew because of weight gain, and 1 withdrew because of shaking). Two people taking fluoxetine plus placebo withdrew (1 because of increased anxiety and 1 because of emotional numbing). [80]

Comment: We found two other RCTs but these did not meet inclusion criteria. [81] [82] The first of these RCTs was not solely in participants who had not responded to serotonin reuptake inhibitors, but also included people who had not responded to venlafaxine or imipramine. [81] The second of these RCTs was excluded because it had a high withdrawal rate (8/26 people [31%]), which exceeded *BMJ Clinical Evidence* criteria for inclusion (< 20% withdrawal). [82]

GLOSSARY

Behavioural therapy Consists of exposure to the anxiety-provoking stimuli, and prevention of ritualistic behaviour (engaging in compulsions).
Chronic obsessive compulsive disorder Continuous course without periods of remission since first onset.
Clinical Global Impression Scale is a one item, observer rated scale for measuring the severity of a condition. It has been investigated for validity and reliability. It is scored on a scale from 0 (not ill at all) to 7 (severely ill).
Cognitive behavioural therapy This is a composite therapy that combines techniques from cognitive therapy and behavioural therapy.
Cognitive therapy Aims to correct distorted thoughts (such as exaggerated sense of harm and personal responsibility) by Socratic questioning, logical reasoning, and hypothesis testing.
Episodic obsessive compulsive disorder Episodic course with periods of remission since first onset.
Exposure homework Tasks involving contact with anxiety provoking situations to be carried out outside regular psychotherapy sessions.
Hamilton Anxiety Rating Scale is a 14 item observer rated scale for measuring the severity of anxiety. It has been investigated for validity and reliability. Each item is rated on a 5 point scale from 0 (no symptoms) to 4 (severe or grossly disabling symptoms). Total score ranges from 0 to 56, with 14 or higher indicating clinically significant anxiety.
Hamilton Depression Rating Scale is a 21 item observer rated scale for measuring the severity of depression. Hamilton recommended that the first 17 items only be used for this purpose, as the last four items do not measure the severity of depression. It has been investigated for validity and reliability. Items are measured on a scale of 0–4 or 0–2 (with a higher score indicating more severe symptoms). Total score ranges from 0 to 50, with a score of 8 or above indicating clinically significant depression.
Maudsley Obsessional Compulsive Inventory is a 30 item self report true–false scale, designed to measure the total frequency of obsessive compulsive disorder symptoms. Although the internal consistency, test–retest reliability, and validity are satisfactory, the scale is relatively insensitive to changes in symptoms.
Schizotypal personality disorder Characterised by discomfort in close relationships, cognitive and perceptual distortions, and eccentric behaviour.
Tic disorder Characterised by motor tics, vocal tics, or both.
Yale–Brown Obsessive Compulsive Scale (YBOCS) is a validated, observer rated scale for measuring symptom scores. It rates the severity of both obsessions and compulsions across five dimensions (time spent, interference with functioning, distress, resistance, and control), each on a 5 point scale from 0 (the dimension is absent) to 4 (dimension is present to an extremely severe degree). The total score range of obsessions and compulsions combined is 0–40 (the higher the score, the more severe the condition). Most trials use a 25% or 35% reduction in YBOCS scores from baseline as indicative of clinically important improvement.

SUBSTANTIVE CHANGES

Behavioural or cognitive therapy plus serotonin reuptake inhibitors: One RCT added; [70] benefits and harms data enhanced, categorisation unchanged (Unknown effectiveness).
Behavioural therapy: One RCT added; [26] benefits and harms data enhanced, categorisation unchanged (Beneficial).
Serotonin reuptake inhibitors (citalopram, clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline): Harms data enhanced; [57] [59] [60] [61] categorisation unchanged (Beneficial).

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TABLE 1 **National surveys of age and sex standardised annual and lifetime prevalence of OCD in people aged 26–64 years.** [5]

Country	Survey size (people)	Annual prevalence	Lifetime prevalence
Canada	2200	1.4%	2.3%
Puerto Rico	1200	1.8%	2.5%
Germany	4811	1.6%	2.1%
Taiwan	7400	0.4%	0.7%
Korea	4000	1.1%	1.9%
New Zealand	1200	1.1%	2.2%

TABLE 2 **Serotonin reuptake inhibitors (clomipramine, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) versus placebo (see text, p 5).**

Intervention and reference	Study design	Symptom improvement
*Citalopram***		
[41]	RCT (401 people)	AR: 57% with citalopram 20 mg *v* 52% with 40 mg *v* 65% with 60 mg *v* 37% with placebo; NNT for 20 mg citalopram *v* placebo 5, 95% CI 3 to 14
Clomipramine¶*		
[37]	SR (9 RCTs; 668 people)	SMD 1.31 (95% CI 1.15 to 1.47)
[38]	SR (7 RCTs; 808 people)	SMD –8.19 (95% CI –10.53 to –5.85)
Fluoxetine†¶		
[37]	SR (1 RCT; 287 people)	SMD 0.57 (95% CI 0.33 to 0.81)
[38]	SR (3 RCTs; 329 people)	SMD –1.61 (95% CI –2.18 to –1.04)
[40]	RCT (350 people)	Mean reduction in score 4.6 with fluoxetine 20 mg, 5.5 with 40 mg, 6.5 with 60 mg *v* 0.9 with placebo (P < 0.001 for all doses *v* placebo)
Fluvoxamine‡		
[37]	SR	SMD 0.57 (95% CI 0.37 to 0.77)
[38]	SR (4 RCTs; 264 people)	SMD –4.84 (95% CI –7.78 to –1.83) (measured as a change in raw score of Yale–Brown)
[42]	RCT (253 people)	Mean reduction in score 8.5 with fluvoxamine controlled release 100–300 mg *v* 5.6 with placebo (P = 0.001)
Paroxetine¶		
[38]	SR (1 RCT; 300 people)	SMD –3.00 (95% CI –4.91 to –1.09)
[39]	RCT (348 people)	Mean reduction in YBOCS score at 12 weeks: 16% with paroxetine 20 mg/day *v* 25% with paroxetine 40 mg/day *v* 29% with paroxetine 60 mg/day *v* 13% with placebo; significantly greater with paroxetine 40 mg or 60 mg than with placebo, paroxetine 20 mg/day *v* placebo: NS; P values and CI not reported
[43]	RCT (191 people)	Mean difference in YBOCS score between paroxetine (20–50 mg/day) and placebo at 12 weeks: -4.52, 95% CI –6.57 to –22.48; P = 0.00002 Proportion of people "much" or "very much" improved on YBOCS item 18 Likert scale at 12 weeks: 47/94 [50%] with paroxetine *v* 22/93 [24%] with placebo; P = 0.0003
Sertraline§¶		
[37]	SR (3 RCTs; 270 people)	SMD 0.52 (95% CI 0.27 to 0.77)
[38]	SR (4 RCTs; 598 people)	SMD –2.57 (95% CI –6.13 to +1.20); NS

*The total number of different RCTs identified was 11; †the total number of different RCTs identified was 5; ‡the total number of different RCTs identified was 6; §the total number of different RCTs identified was 4; ¶ symptoms assessed by YBOCS score; ** > 25% reduction in YBOCS score. NS, not significant; YBOCS, Yale–Brown Obsessive Compulsive Scale

TABLE 3 **Serotonin reuptake inhibitors versus each other (see text, p 5).**

Study type and reference	Number of people	Comparison	Results
SR (3 RCTs) [37]	85	Clomipramine *v* fluoxetine or fluvoxamine	SMD –0.04, 95% CI –0.43 to + 0.35
SR [38]	Clomipramine *v* fluvoxamine (4 RCTs; 175 people); clomipramine *v* fluoxetine (1 RCT; 55 people); clomipramine *v* paroxetine (1 RCT; 300 people)	Clomipramine *v* fluvoxamine or fluoxetine or paroxetine	Clomipramine *v* fluvoxamine pooled change in YBOCS score: SMD + 1.23, 95% CI –1.11 to + 3.56; clomipramine *v* fluoxetine change Yale-Brown Compulsive Scale score: SMD + 1.40, 95% C1 –5.74 to + 2.94; clomipramine *v* paroxetine change in YBOCS score: SMD 0, 95% CI –1.94 to + 1.94
RCT [44]	170	Sertraline *v* clomipramine	Mean reduction in Yale-Brown Scale score: 8%; P = 0.036
RCT [45]	133	Clomipramine *v* fluvoxamine	Change in YBOCS score: 12.6 with clomipramine *v* 12.3 with fluvoxamine; reported as not significant; no further data reported
RCT [46]	227	Clomipramine (150–300 mg) *v* fluvoxamine (150–300 mg)	Mean reduction in YBOCS score: about 12 in both groups; P value not reported; proportion of people achieving at least 35% reduction in YBOCS score: 65% with clomipramine *v* 62% with fluvoxamine; reported as not significant
RCT [47]	150	Sertraline (50–200 mg) *v* fluoxetine (20–80 mg	Reduction in YBOCS score: 9.6 with sertraline *v* 9.7 with fluoxetine; CI not reported
RCT [48]	30	Fluvoxamine *v* paroxetine *v* citalopram	Mean reduction in Yale-Brown Scale score: 36% with fluvoxamine *v* 29% with paroxetine *v* 32% with citalopram; reported as not significant; CI not reported

YBOCS, Yale–Brown Obsessive Compulsive Scale.