Interventions for obsessive compulsive symptoms in people with schizophrenia

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. Primary objectives—To evaluate clinically meaningful benefits of interventions used to treat clinically significant obsessive compulsive symptoms occurring in people with schizophrenia with regard to global improvement, changes in mental state, hospitalisation, behaviour and functioning in the short term (less than six weeks), medium term (six weeks to six months) and long term (more than six months).

In this review we specifically addressed the efficacy and safety of the following when used to treat clinically significant obsessive compulsive symptoms occurring in people with schizophrenia:

- 1.1 Conventional and newer (or atypical) antipsychotic drugs
- 1.2 Conventional and newer antidepressant drugs
- 1.3 Any other drug or pharmacologically active substance
- 1.4 Non-pharmacological interventions

In future versions of this review we will cover the use of psychosurgery, deep brain stimulation or other invasive interventions for this purpose.

2. Secondary objectives—To determine whether these interventions would have a differential effect:

- 2.1 In people with schizophrenia in whom obsessive compulsive symptoms preceded the onset of symptoms of schizophrenia as opposed to those in whom obsessive compulsive symptoms occurred in the prodromal stages or after the symptoms of schizophrenia were firmly established
- 2.2 In people with obsessive compulsive symptoms as opposed to obsessive compulsive disorder as defined by diagnostic criteria

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Editorial group: Cochrane Schizophrenia Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

CONTRIBUTIONS OF AUTHORS

Both reviewers developed the protocol.

DECLARATIONS OF INTEREST

None known.

BACKGROUND

Surveys conducted amongst people with schizophrenia show an estimated prevalence of co-morbid obsessive compulsive symptoms ranging from 8% to 46% (Craig 2002, Fenton 1986, Poyurovsky 1999, Poyurovsky 2001, Tibbo 2000). Approximately 15% to 30% meet diagnostic criteria for obsessive compulsive disorder (OCD) (Bermanzohn 2000, de Hann 2002a, Nechmad 2003). These rates are considerably higher than the 1.2 to 2.5% prevalence of obsessive compulsive disorder seen in the general population worldwide (Weissman 1994). Both OCD and schizophrenia often have their onset in adolescence, and both disorders often follow an episodic or chronic course, with considerable accompanying distress and disability (Steketee 1997). Obsessive compulsive symptoms may precede the onset of schizophrenia, occur in the prodromal phase, or appear during the course of the illness. The use of atypical antipsychotics has been associated with the emergence or worsening of obsessive compulsive symptoms; the drugs implicated in case series include clozapine (de Haan 1999, Robert 1992), olanzapine (Lykouras 2000), risperidone (Alevizos 2002) and quetiapine (Khullar 2001). However, prospective systematic surveys have not confirmed the propensity of risperidone or olanzapine to induce or exacerbate obsessive compulsive symptoms (Baker 1996, de Hann 2002a).

People with schizophrenia and co-morbid obsessive compulsive symptoms are generally characterised by: lower levels of social functioning, longer duration of hospitalisation, more neurocognitive impairment, greater severity of negative symptoms, greater propensity to develop extrapyramidal effects and treatment resistance than those without obsessive compulsive symptoms. (Fenton 1986, Eisen 1997, Hwang 2000, Kruger 2000, Poyurovsky 2001, Lysaker 2000, Lysaker 2002, Ohta 2003).

Obsessive compulsive disorder is commonly treated by antidepressant drugs, the talking therapies, sometimes antipsychotics and very rarely, psychosurgery, using stereotaxic techniques (Lopez 2004), or the more recent technique of deep brain stimulation (Nuttin 2003), also has reported benefits. Uncontrolled reports of the benefits of the antidepressant clomipramine and SSRI class of antidepressants in treating people with schizophrenia and co-morbid OCD are encouraging (Berman 1995, Khan 2004). However, atypical antipsychotics, though sometimes implicated in the emergence or worsening of obsessive compulsive symptoms, have also been effectively used to reduce these symptoms when used as the sole treatment (Poyurovsky 2000, Veznedaroglu 2003, Kumar 2003, Reznik 2004), or when used in conjunction with serotonergic drugs (Strous 1999, Reznik 2000, Poyurovsky 2003). Both SS-RIs (Poyurovsky 1996) and behavioural therapy (MacCabe 2002) have been used to effectively treat obsessive compulsive symptoms occurring after treatment with atypical antipsychotics.

The treatment strategy for those with schizophrenia who also experience obsessive compulsive symptoms or OCD remains unclear, and in this review we have attempted to answer the following questions. Would conventional or atypical antipsychotics be effective in treating those in whom these symptoms occur after the symptoms of schizophrenia have been established? Would these drugs be effective in those whose obsessive compulsive symptoms preceded the onset of schizophrenia? Would the dose of these drugs matter in

treating obsessive compulsive symptoms, or would there be differences in the efficacy of conventional versus atypical drugs or between drugs from the same class? Would a combination of antipsychotic drugs and interventions that are effective in primary OCD be effective in those with schizophrenia and OCD? What would be the effect of these interventions on the core positive (delusions, hallucinations and disturbances in thinking) and negative (poor motivation, poor communication, poor socialisation and poor emotional response) symptoms of schizophrenia? Would they be equally effective late as opposed to early on in the course of schizophrenia?

Technical background

Neuro-imaging studies have revealed many common as well as dissimilar areas of structural changes in the brains of people with schizophrenia with and without OCD, and those with OCD compared to normal controls, chiefly involving the hippocampus; basal ganglia, in particular the caudate nucleus; the orbitofrontal cortex; the anterior cingulate gyrus and the medio-dorsal thalamic nucleus (Aoyama 2000, Gross-Isseroff 2003, Kim 2003, Kurokawa 2000, Kwon 2003). These common abnormalities, detected even early in the course of the disorder, and the overlap in the clinical presentations of these conditions, suggest a common neuro-developmental origin for these conditions and provide the basis for the suggestion that people with schizophrenia and co-morbid OCD may have a distinct subtype of schizophrenia that some have called 'schizo-obsessive disorder' or 'obsessive-compulsive schizophrenia'. It is also possible that even among people with schizophrenia and comorbid OCD, there are subgroups defined by time of onset of schizophrenia in the course of the disorder and by other clinical or biological parameters (Lysaker 2004).

Obsessive compulsive disorder is commonly treated by drugs that act selectively or primarily on the neuro-transmitter called serotonin. Clomipramine and the selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, are the first line treatments for people with OCD and are thought to be superior to anti-depressant drugs with no serotonergic properties (Piccinelli 1995). However, 40-60% of patients with obsessive compulsive disorder do not respond to adequate treatment with SSRIs or clomipramine (Kaplan 2003), and agents that alter serotonin receptors and other neurotransmitter systems, such as dopamine, norepinephrine, and second-messenger systems, may also play a role in treatment. More commonly, non-pharmacological methods such as behaviour therapy (BT) and cognitive behaviour therapy (CBT) are used, either alone or in conjunction with clomipramine or SSRIs. Behaviour therapy is a specific technique where the person is exposed to stimuli that provoke obsessive thoughts but is prevented from making the compulsive response (exposure and response prevention or ERP) (Abramowitz 1997, Kobak 1998, McLean 2001). For those failing to show adequate response to any of these interventions, psychosurgery (Lopez 2004), or deep brain stimulation (Nuttin 2003), also has reported benefits.

OBJECTIVES

1. Primary objectives

To evaluate clinically meaningful benefits of interventions used to treat clinically significant obsessive compulsive symptoms occurring in people with schizophrenia with regard to global improvement, changes in mental state, hospitalisation, behaviour and functioning in the short term (less than six weeks), medium term (six weeks to six months) and long term (more than six months).

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METHODS

Criteria for considering studies for this review

Types of studies—We included all relevant randomised controlled trials. Where a trial was described as ‘double-blind’, but it was only implied that the study was randomised, we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes (see types of outcome measures) when these ‘implied randomisation’ studies were added, then we included these in the final analysis. If there was a substantive difference, we used only those trials that were clearly randomised and described the results of the sensitivity analysis in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants—We included people with schizophrenia of all ages, diagnosed by any criteria, who also show obsessive compulsive symptoms, however diagnosed.

Types of interventions—1.1 Antipsychotic drugs: conventional or atypical

1.2 Antidepressant drugs: tricyclics, specific serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, mono-amine-oxidase inhibitors, other antidepressants.

1.3 Any other drug or pharmacologically active substance

1.4 Placebo

1.5 Behaviour therapy

1.6 Cognitive behaviour therapy

1.7 Other non-pharmacological interventions

It is expected that everyone in the studies would also be receiving antipsychotic medication with or without an anticholinergic drug for extrapyramidal symptoms.

Types of outcome measures

Primary outcomes: 1. No clinical response

1.1 No clinically significant response in global state - as defined by each of the studies

1.2 No clinically significant response on psychotic symptoms - as defined by each of the studies

1.3 No clinically significant response on obsessive compulsive symptoms - as defined by each of the studies

2. Adverse effects, general and specific

Secondary outcomes: 1. Death - suicide or natural causes

2. Leaving the study early or dropouts

3. No clinical response

3.1 Average score/change in global state

3.2 Average score/change on psychotic symptoms

3.3 Average score/change in obsessive compulsive symptoms

4. Extrapyramidal side effects

4.1 Use of anticholinergic drugs

4.2 No clinically significant extrapyramidal side effects - as defined by each of the studies

4.3 Average score/change in extrapyramidal side effects

6. Service utilisation outcomes

6.1 Hospital admission

6.2 Days in hospital

7. Economic outcomes

8. Quality of life / satisfaction with care for either recipients of care or carers

8.1 No significant change in quality of life / satisfaction - as defined by each of the studies

8.2 Average score / change in quality of life / satisfaction

Search methods for identification of studies

Electronic searches—We searched the Cochrane Schizophrenia Group's Trials Register (December 2004) using the phrase:

[(**obsessi** or **compulsi** or **YBOCS** or **Y-BOCS**) in title, abstract and index terms in REFERENCE) and ((**obsessi** or **compulsi**) in outcomes in STUDY)]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module). No language restrictions will be used for electronic searches.

Searching other resources

1. Citation searching: We inspected the citation lists from all identified studies for additional studies.

2. Personal contact: We contacted the first author of each included study published during the last ten years for additional references and for any unpublished trials.

3. Pharmaceutical companies: We contacted companies involved in the production of the principal antipsychotic, antidepressant and anti-obsessional drugs and requested additional studies.

4. Citations: We sought all selected studies as citations on the ISI database in order to identify more trials.

Data collection and analysis

1. Selection of trials—Two reviewers (RM, SF) independently inspected the citations identified from the search. Potentially relevant abstracts were identified and full papers ordered and reassessed for inclusion and methodological quality. Any disagreement during this process was discussed and reported.

2. Assessment of methodological quality—Trials were allocated to three quality categories, as described in the Cochrane Collaboration Handbook (Clarke 2001) by each reviewer, again, working independently. When disputes arose as to which category a trial was allocated to, resolution was attempted by discussion. When this was not possible, and further information was necessary, data were not entered into the analyses and the study was allocated to the list of those awaiting assessment. Only trials in Category A or B were included in the review.

3. Data management

3.1 Data extraction: We independently extracted data from each selected report and attempted to resolve any disagreement by discussion. Where disagreement persisted, or if published results made data extraction difficult, we attempted to obtain clarification from the authors of the trial, pending which we assigned the trial to those awaiting assessment.

3.2 Binary outcomes: We excluded binary data if more than 50% of people were lost to follow up. Where binary outcomes (proportions) are used, we calculated relative risks (RR), fixed and 95% confidence intervals for each outcome. In addition we calculated absolute measures, the number needed to treat (NNT) and, if appropriate, the number needed to harm (NNH) with their 95% confidence intervals. We undertook analyses on an intention to treat basis.

3.3 Continuous outcomes: We excluded continuous data if more than 50% of people were lost to follow up. We reported continuous data as presented in the original studies, without making any assumptions about those lost to follow up. We calculated pooled weighted mean differences (WMD) along with confidence intervals, for outcomes using similar scales.

3.3.1 Validity of continuous measures: We only included continuous data from rating scales if the measuring instrument had been described in a peer-reviewed journal and the instrument was either a self report, or completed by an independent rater or relative (not the therapist). Unpublished instruments are more likely to report statistically significant findings than those that have been peer reviewed and published (Marshall 2000).

3.4 Leaving the study early: People dropped out of each of the studies of their own volition or as a result of a decision made by the trialists. For binary outcomes, we assigned people who left of their own accord to the least favourable outcome group. We tested the effects of this assignment in a sensitivity analysis.

3.5 Normal distribution of continuous data: Data on continuous outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, all data included in the review met the following criteria:

- i. standard deviations and means were reported in the paper or were obtainable from the authors;
- ii. when a scale started from 0 the standard deviation (SD), when multiplied by two was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution (Altman 1996).

- iii. if a scale started from a positive value (such as PANSS that can have values from 30 to 210) the calculation described above in ii) was modified to take the scale starting point into account. In these cases skewness was considered present if $2SD > (S - S_{min})$, where S is the mean score and S_{min} is the minimum score.

Data that did not meet these standards were not entered into the RevMan software (which assumes a normal distribution). However, we reported data not meeting these criteria in additional tables and in the text, if they had been analysed with appropriate non-parametric tests.

3.6 Endpoint versus change data: Where possible we presented endpoint data and if both endpoint and change data are available for the same outcomes then we only reported the former.

3.7 Cluster trials: Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra class correlation co-efficients of their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect. We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation co-efficient (ICC) Design effect = $1 + (m - 1) * ICC$ (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999).

3.8 Presentation of data: Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for the intervention of interest. For some scales a high score indicates a bad outcome, but for others, high scores are good. When the latter was the case the area to the left of the line indicates a favourable outcome for the control group and is so labelled.

4. Heterogeneity—After considering the likelihood of clinical heterogeneity based on comparisons of the included studies, we visually inspected graphs to investigate the possibility of statistical heterogeneity. We calculated the value of I-squared to provide an estimate of the percentage of variability due to heterogeneity rather than chance alone. We interpreted an I-squared value of 50% or greater as indicating high levels of heterogeneity (Higgins 2003, Deeks 2004). If inconsistency was high, we did not summate data, but presented it separately and investigated the reasons for heterogeneity. In any event, if

substantial heterogeneity was present, we undertook a sensitivity analysis to the presence or absence of these data.

5. Sensitivity and subgroup analysis—We undertook sensitivity analyses in all instances when heterogeneity was detected. The effect of including studies with high attrition rates was analysed in a sensitivity analysis. In addition, we detected the differences in outcomes for (a) for people with schizophrenia in whom obsessive compulsive symptoms preceded the onset of symptoms of schizophrenia, as opposed to those in whom obsessive compulsive symptoms occurred in the prodromal stages or after the symptoms of schizophrenia were established, (b) for people with schizophrenia as opposed to those with schizo-affective disorder, (c) for people with obsessive compulsive symptoms as opposed to obsessive compulsive disorder as defined by diagnostic criteria, and (d) when interventions are used in combination rather than individually.

6. Publication bias—When outcomes include data from five or more trials, we entered data into a funnel graph (trial effect versus trial size) in an attempt to investigate the likelihood of overt publication bias.

Acknowledgments

None.

SOURCES OF SUPPORT

Internal sources

- Post Graduate Institute, Lady Reading Hospital, Peshawar, Pakistan.

External sources

- No sources of support supplied

WHAT'S NEW

Date	Event	Description
27 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2005

Additional references

- Abramowitz 1997 . Abramowitz JS. Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. *Journal of Consulting and Clinical Psychology*. 1997; 65:44–52. [PubMed: 9103733]
- Alevizos 2002 . Alevizos B, Lykouras L, Zervas IM, Christodoulou GN. Risperidone-induced obsessive-compulsive symptoms: a series of six cases. *Journal of Clinical Psychopharmacology*. 2002; 22:461–7. [PubMed: 12352268]
- Altman 1996 . Altman DG, Bland JM. Detecting skewness from summary information. *BMJ*. 1996; 313:1200. [OLZ020600]. [PubMed: 8916759]

- Aoyama 2000 . Aoyama F, Iida J, Inoue M, Iwasaka H, Sakiyama S, Hata K, et al. Brain imaging in childhood and adolescence-onset schizophrenia associated with obsessive compulsive symptoms. *Acta Psychiatrica Scandinavica*. 2000; 102:32–7.
- Baker 1996 . Baker RW, Ames D, Umbricht DS, Chengappa KN, Schooler NR. Obsessive-compulsive symptoms in schizophrenia: a comparison of olanzapine and placebo. *Psychopharmacology Bulletin*. 1996; 32:89–93. [PubMed: 8927681]
- Berman 1995 . Berman I, Sapers BL, Chang HH, Losonczy MF, Schmiedler J, Green AI. Treatment of obsessive-compulsive symptoms in schizophrenic patients with clomipramine. *Journal of Clinical Psychopharmacology*. 1995; 15:206–10. [PubMed: 7635998]
- Bermanzohn 2000 . Bermanzohn PC, Porto L, Arlow PB, Pollack S, Stronger R, Siris SG. Hierarchical diagnosis in chronic schizophrenia: a clinical study of co-occurring syndromes. *Schizophrenia Bulletin*. 2000; 26:517–25. [PubMed: 10993392]
- Bland 1997 . Bland JM. Statistics notes. Trials randomised in clusters. *BMJ*. 1997; 315:600. [PubMed: 9302962]
- Clarke 2001 . Clarke M, Oxman AD. *The Cochrane Collaboration Handbook*. The Cochrane Library. 2001; (1)
- Craig 2002 . Craig T, Hwang MY, Bromet EJ. Obsessive-compulsive and panic symptoms in patients with first-admission psychosis. *American Journal of Psychiatry*. 2002; 159:592–8. [PubMed: 11925297]
- de Haan 1999 . de Haan L, Linszen DH, Gorsira R. Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. *Journal of Clinical Psychiatry*. 1999; 60:364–5. [PubMed: 10401913]
- de Hann 2002a . de Haan L, Beuk N, Hoogenboom B, Dingemans P, Linszen D. Obsessive-compulsive symptoms during treatment with olanzapine and risperidone: a prospective study of 113 patients with recent-onset schizophrenia or related disorders. *Journal of Clinical Psychiatry*. 2002; 63:104–7. [PubMed: 11874209]
- Deeks 2004 . Deeks JJ, Higgins JPT, Altman DG, editors. *Cochrane Reviewers' Handbook 4.2.2* [updated December 2003]. In: *The Cochrane Library*. 2004. Analysing and presenting results.
- Divine 1992 . Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine*. 1992; 7(6):623–9. [PubMed: 1453246]
- Donner 2002 . Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine*. 2002; 21:2971–80. [PubMed: 12325113]
- Eisen 1997 . Eisen JL, Beer DA, Pato MT, Venditto TA, Rasmussen SA. Obsessive-Compulsive Disorder in patients with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*. 1997; 154:271–3. [PubMed: 9016282]
- Fenton 1986 . Fenton WS, McGlashan TH. The prognostic significance of obsessive-compulsive symptoms in schizophrenia. *American Journal of Psychiatry*. 1986; 143:437–41. [PubMed: 3953886]
- Gross-Isseroff 2003 . Gross-Isseroff R, Hermesh H, Zohar J, Weizman A. Neuroimaging communality between schizophrenia and obsessive compulsive disorder: a putative basis for schizo-obsessive disorder? *World Journal of Biological Psychiatry*. 2003; 4:129–34. [PubMed: 12872207]
- Gulliford 1999 . Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology*. 1999; 149:876–83. [PubMed: 10221325]
- Higgins 2003 . Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60. [PubMed: 12958120]
- Hwang 2000 . Hwang MY, Morgan JE, Losonczy MF. Clinical and neuropsychological profiles of obsessive-compulsive schizophrenia: a pilot study. *Journal of Neuropsychiatry and Clinical Neuroscience*. 2000; 12:91–4.
- Kaplan 2003 . Kaplan A, Hollander E. A Review of Pharmacologic Treatments for Obsessive-Compulsive Disorder. *Psychiatric Services*. 2003; 54:1111–8. [PubMed: 12883138]

- Khan 2004 . Khan MNS, Arshad N, Ullah N. Treatment outcome of schizophrenia co-morbid with obsessive-compulsive disorder. *Journal of the College of Physicians and Surgeons of Pakistan*. 2004; 14:234–6.
- Khullar 2001 . Khullar A, Chue P, Tibbo P. Quetiapine and obsessive-compulsive symptoms (OCS): case report and review of atypical antipsychotic-induced OCS. *Journal of Psychiatry and Neuroscience*. 2001; 26:55–9. [PubMed: 11212595]
- Kim 2003 . Kim JJ, Youn T, Lee JM, Kim IY, Kim SI, Kwon JS. Morphometric abnormality of the insula in schizophrenia: a comparison with obsessive-compulsive disorder and normal control using MRI. *Schizophrenia Research*. 2003; 60:191–8. [PubMed: 12591583]
- Kobak 1998 . Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. *Psychopharmacology*. 1998; 136:205–16. [PubMed: 9566805]
- Kruger 2000 . Kruger S, Braunig P, Hoffler J, Shugar G, Borner I, Langkrar. Prevalence of obsessive-compulsive disorder in schizophrenia and significance of motor symptoms. *Journal of Neuro-psychiatry and Clinical Neuroscience*. 2000; 12:16–24.
- Kumar 2003 . Kumar S, Ng B, Howie W. The improvement of obsessive-compulsive symptoms in a patient with schizophrenia treated with clozapine. *Psychiatry and Clinical Neuroscience*. 2003; 57:235–6.
- Kurokawa 2000 . Kurokawa K, Nakamura K, Sumiyoshi T, Hagino H, Yotsutsuji T, Yamashita I, et al. Ventricular enlargement in schizophrenia spectrum patients with prodromal symptoms of obsessive-compulsive disorder. *Psychiatry Research*. 2000; 99:83–91. [PubMed: 10963984]
- Kwon 2003 . Kwon JS, Shin YW, Kim CW, Kim YI, Youn T, Han MH, et al. Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygdala complex. *Journal of Neurology Neurosurgery and Psychiatry*. 2003; 74:962–4.
- Lopez 2004 . Lopes AC, Soares KVS, Del Porto JA. Surgery for obsessive compulsive disorder (Protocol for a Cochrane Review). *Cochrane Database of Systematic Reviews*. 2004; (2) [DOI: 10.1002/14651858.CD001314.pub2].
- Lykouras 2000 . Lykouras L, Zervas IM, Gournellis R, Malliori M, Rabavilas A. Olanzapine and obsessive-compulsive symptoms. *European Neuropsychopharmacology*. 2000; 10:385–7. [PubMed: 10974610]
- Lysaker 2000 . Lysaker PH, Marks KA, Picone JB, Rollins AL, Fastenau PS, Bond GR. Obsessive and compulsive symptoms in schizophrenia: clinical and neurocognitive correlates. *Journal of Nervous and Mental Diseases*. 2000; 188:78–83.
- Lysaker 2002 . Lysaker PH, Bryson GJ, Marks KA, Greig TC, Bell MD. Association of obsessions and compulsions in schizophrenia with neurocognition and negative symptoms. *Journal of Neuropsychiatry and Clinical Neuroscience*. 2002; 14:449–53.
- Lysaker 2004 . Lysaker PH, Lancaster RS, Nees MA, Davis LW. Patterns of obsessive-compulsive symptoms and social function in schizophrenia. *Psychiatry Research*. 2004; 125:139–46. [PubMed: 15006437]
- MacCabe 2002 . MacCabe JH, Marks IM, Murray RM. Behavior therapy attenuates clozapine-induced obsessions and compulsions. *Journal of Clinical Psychiatry*. 2002; 63:1179–80. [PubMed: 12530414]
- Marshall 2000 . Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry*. 2000; 176:249–52. [PubMed: 10755072]
- McLean 2001 . McLean PD, Whittal ML, Thordarson DS, Taylor S, Sochting I, Koch WJ, et al. Cognitive versus behavior therapy in the group treatment of obsessive-compulsive disorder. *Journal of Consulting and Clinical Psychology*. 2001; 69:205–14. [PubMed: 11393598]
- Nechmad 2003 . Nechmad A, Ratzoni G, Poyurovsky M, Meged S, Avidan G, Fuchs C, et al. Obsessive-Compulsive Disorder in Adolescent Schizophrenia Patients. *American Journal of Psychiatry*. 2003; 160:1002–4. [PubMed: 12727709]

- Nuttin 2003 . Nuttin BJ, Gabriels LA, Cosyns PR, Meyerson BA, Andreewitch S, Sunaert SG, et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*. 2003; 52:1263–72. discussion 1272–4. [PubMed: 12762871]
- Ohta 2003 . Ohta M, Kokai M, Morita Y. Features of obsessive-compulsive disorder in patients primarily diagnosed with schizophrenia. *Psychiatry and Clinical Neuroscience*. 2003; 57:67–74.
- Piccinelli 1995 . Piccinelli M, Pini S, Bellantuono C, Wilkinson G. Efficacy of drug treatment in obsessive-compulsive disorder: a meta-analytic review. *British Journal of Psychiatry*. 1995; 166:424–43. [PubMed: 7795913]
- Poyurovsky 1996 . Poyurovsky M, Hermesh H, Weizman A. Fluvoxamine treatment in clozapine-induced obsessive-compulsive symptoms in schizophrenic patients. *Journal of Clinical Neuropharmacology*. 1996; 19:305–13.
- Poyurovsky 1999 . Poyurovsky M, Fuchs C, Weizman A. Obsessive-compulsive disorder in patients with first-episode schizophrenia. *American Journal of Psychiatry*. 1999; 156:1198–2000.
- Poyurovsky 2000 . Poyurovsky M, Dorfman-Etrog P, Hermesh H, Munitz H, Tollefson GD, Weizman A. Beneficial effect of olanzapine in schizophrenic patients with obsessive-compulsive symptoms. *International Clinical Psychopharmacology*. 2000; 15:169–73. [PubMed: 10870875]
- Poyurovsky 2001 . Poyurovsky M, Hramenkov S, Isakov V, Rauchverger B, Modai I, Schneidman M, et al. Obsessive-compulsive disorder in hospitalized patients with chronic schizophrenia. *Psychiatry Research*. 2001; 102:49–57. [PubMed: 11368839]
- Poyurovsky 2003 . Poyurovsky M, Kurs R, Weizman A. Olanzapine-sertraline combination in schizophrenia with obsessive-compulsive disorder. *Journal of Clinical Psychiatry*. 2003; 64:611. [PubMed: 12755669]
- Reznik 2000 . Reznik I, Sirota P. An open study of fluvoxamine augmentation of neuroleptics in schizophrenia with obsessive and compulsive symptoms. *Clinical Neuropharmacology*. 2000; 23:157–60. [PubMed: 10895399]
- Reznik 2004 . Reznik I, Yavin I, Stryker R, Spivak B, Gonen N, Strous R, et al. Clozapine in the treatment of obsessive-compulsive symptoms in schizophrenia patients: a case series study. *Pharmacopsychiatry*. 2004; 37:52–6. [PubMed: 15048611]
- Robert 1992 . Robert WB, Chengappa R, James WB. Emergence of obsessive compulsive symptoms during treatment with clozapine. *Journal of Clinical Psychiatry*. 1992; 53:439–42. [PubMed: 1487472]
- Steketee 1997 . Steketee G. Disability and family burden in obsessive-compulsive disorder. *Canadian Journal of Psychiatry*. 1997; 42:919–28.
- Strous 1999 . Strous RD, Patel JK, Zimmet S, Green AI. Clozapine and paroxetine in the treatment of schizophrenia with obsessive-compulsive features. *American Journal of Psychiatry*. 1999; 156:973–4. [PubMed: 10360153]
- Tibbo 2000 . Tibbo P, Kroetsch M, Chue P, Warneke L. Obsessive-compulsive disorder in schizophrenia. *Journal of Psychiatric Research*. 2000; 34:39–46.
- Ukoumunne 1999 . Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review. *Health Technology Assessment*. 1999; 3(5):iii–92. [MEDLINE: 10982317]. [PubMed: 10982317]
- Veznedaroglu 2003 . Veznedaroglu B, Ercan ES, Kayahan B, Varan A, Bayraktar E. Reduced short-term obsessive-compulsive symptoms in schizophrenic patients treated with risperidone: a single-blind prospective study. *Human Psychopharmacology*. 2003; 18:635–40. [PubMed: 14696023]
- Weissman 1994 . Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu H, Lee CK, et al. The cross national epidemiology of obsessive compulsive disorder - the Cross National Collaborative Group. *Journal of Clinical Psychiatry*. 1994; 55(3 Suppl):5–10. [PubMed: 8077177]

* Indicates the major publication for the study