Pharmacological interventions for borderline personality disorder (Review)

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[Intervention Review]

Pharmacological interventions for borderline personality disorder

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ABSTRACT

Background

Drugs are widely used in borderline personality disorder (BPD) treatment, chosen because of properties known from other psychiatric disorders ("off-label use"), mostly targeting affective or impulsive symptom clusters.

Objectives

To assess the effects of drug treatment in BPD patients.

Search strategy

We searched bibliographic databases according to the Cochrane Developmental, Psychosocial and Learning Problems Group strategy up to September 2009, reference lists of articles, and contacted researchers in the field.

Selection criteria

Randomised studies comparing drug versus placebo, or drug versus drug(s) in BPD patients. Outcomes included total BPD severity, distinct BPD symptom facets according to DSM-IV criteria, associated psychopathology not specific to BPD, attrition and adverse effects.

Data collection and analysis

Two authors selected trials, assessed quality and extracted data, independently.

Main results

Twenty-eight trials involving a total of 1742 trial participants were included. First-generation antipsychotics (flupenthixol decanoate, haloperidol, thiothixene); second-generation antipsychotics (aripirazole, olanzapine, ziprasidone), mood stabilisers (carbamazepine, valproate semisodium, lamotrigine, topiramate), antidepressants (amitriptyline, fluoxetine, fluvoxamine, phenelzine sulfate, mianserin), and dietary supplementation (omega-3 fatty acid) were tested. First-generation antipsychotics were subject to older trials, whereas recent

studies focussed on second-generation antipsychotics and mood stabilisers. Data were sparse for individual comparisons, indicating marginal effects for first-generation antipsychotics and antidepressants.

The findings were suggestive in supporting the use of second-generation antipsychotics, mood stabilisers, and omega-3 fatty acids, but require replication, since most effect estimates were based on single studies. The long-term use of these drugs has not been assessed.

Adverse event data were scarce, except for olanzapine. There was a possible increase in self-harming behaviour, significant weight gain, sedation and changes in haemogram parameters with olanzapine. A significant decrease in body weight was observed with topiramate treatment. All drugs were well tolerated in terms of attrition.

Direct drug comparisons comprised two first-generation antipsychotics (loxapine versus chlorpromazine), first-generation antipsychotic against antidepressant (haloperidol versus amitriptyline; haloperidol versus phenelzine sulfate), and second-generation antipsychotic against antidepressant (olanzapine versus fluoxetine). Data indicated better outcomes for phenelzine sulfate but no significant differences in the other comparisons, except olanzapine which showed more weight gain and sedation than fluoxetine. The only trial testing single versus combined drug treatment (olanzapine versus olanzapine plus fluoxetine; fluoxetine versus fluoxetine plus olanzapine) yielded no significant differences in outcomes.

Authors' conclusions

The available evidence indicates some beneficial effects with second-generation antipsychotics, mood stabilisers, and dietary supplementation by omega-3 fatty acids. However, these are mostly based on single study effect estimates. Antidepressants are not widely supported for BPD treatment, but may be helpful in the presence of comorbid conditions. Total BPD severity was not significantly influenced by any drug. No promising results are available for the core BPD symptoms of chronic feelings of emptiness, identity disturbance and abandonment. Conclusions have to be drawn carefully in the light of several limitations of the RCT evidence that constrain applicability to everyday clinical settings (among others, patients' characteristics and duration of interventions and observation periods).

PLAIN LANGUAGE SUMMARY

Drug treatment for borderline personality disorder

Many people with borderline personality disorder (BPD) receive medical treatment. However, there are no drugs available for BPD treatment specifically. A certain drug is most often chosen because of its known properties in the treatment of associated disorders, or BPD symptoms that are also known to be present in other conditions, such as depressive, psychotic, or anxious disorders. BPD itself is characterised by a pervasive pattern of instability in affect regulation (with symptoms such as inappropriate anger, chronic feelings of emptiness, and affective instability), impulse control (symptoms: self-mutilating or suicidal behaviour, ideation, or suicidal threats to others), interpersonal problems (symptoms: frantic efforts to avoid abandonment, patterns of unstable relationships with idealization and depreciation of others), and cognitive-perceptual problems (symptoms: identity disturbance in terms of self perception, transient paranoid thoughts or feelings of dissociation in stressful situations). This review aimed to summarise the current evidence of drug treatment effects in BPD from high-quality randomised trials.

Available studies tested the effects of antipsychotic, antidepressant and mood stabiliser treatment in BPD. In addition, the dietary supplement omega-3 fatty acid (commonly derived from fish) which is supposed to have mood stabilising effects was tested. Twenty-eight studies covering 1742 study participants were included.

The findings tended to suggest a benefit from using second-generation antipsychotics, mood stabilisers, and omega-3 fatty acids, but most effect estimates were based on single study effects so repeat studies would be useful. Moreover, the long-term use of these drugs has not been assessed. The small amount of available information for individual comparisons indicated marginal effects for first-generation antipsychotics and antidepressants.

The data also indicated that there may be an increase in self-harming behaviour in patients treated with olanzapine. In general, attention must be paid to adverse effects. Most trials did not provide detailed data of adverse effects and thus could not be considered within this review. We assumed their effects were similar to those experienced by patients with other conditions. Available data of the studies included here suggested adverse effects included weight gain, sedation and change of haemogram parameters with olanzapine treatment, and weight loss with topiramate. Very few beneficial effects were identified for first-generation antipsychotics and antidepressants. However, they may be helpful in the presence of comorbid problems that are not part of BPD core pathology, but can often be found in BPD patients.

There are only few study results per drug comparison, with small numbers of included participants. Thus, current findings of trials and this review are not robust and can easily be changed by future research endeavours. In addition, the studies may not adequately reflect several characteristics of clinical settings (among others, patients' characteristics and duration of interventions and observation periods).

BACKGROUND

The disorder is a condition first recognised in the 19th century. The term 'Borderline Personality Disorder' (BPD) was coined by A. Stern describing a condition in the "borderland" between psychosis and neurosis (Stern 1938). Subsequent psychoanalytic contributions (especially that of Kernberg 1975) have reaffirmed this distinction emphasising that the capacity to test reality remains grossly intact but is subject to subtle distortions, especially under stress.

According to current diagnostic criteria, BPD is characterised by a pervasive pattern of instability in affect regulation, impulse control, interpersonal relationships, and self-image. Clinical hallmarks include emotional dysregulation, impulsive aggression, repeated self-injury, and chronic suicidal tendencies (Lieb 2004). Whereas some authors have suggested that it is a variant of affective disorders (Akiskal 2004), others claim only partially overlapping etiologies (Paris 2007). Despite the difficulties in defining the condition, borderline personality disorder is the focus of great interest. Its importance stems from the huge suffering of the persons concerned, functional impairment (Skodol 2002), and from the significant impact it has on mental health services (Zanarini 2004a).

The definition of BPD in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV, also DMS-IV-TR; APA 1994; APA 2000a) comprises nine criteria that cover the above features, with a definite diagnosis requiring that five criteria are met, and probable diagnosis requiring four. The competing International Classification of Diseases in its 10th edition (ICD-10) refers to the condition of Emotionally Unstable Personality Disorder (F60.3) of which there is an impulsive type (F60.30) and a borderline type (F60.31) (WHO 1993). The latter essentially overlaps with the DSM-IV definition. A significant problem with this type of polythetic definition is that it is possible for two people to satisfy the criteria and yet have very different personalities. This heterogeneity is a major problem in assessing the impact of an intervention. In addition to the specific BPD criteria, DSM-IV and ICD-10 provide general diagnostic criteria for personality disorders that also must be met.

The prevalence of BPD is estimated to be about 1.5% in the general population (most recent data: Lenzenweger 2007; for a survey of epidemiologic studies see Torgersen 2005), but higher (up to 20%) among psychiatry inpatients, and predominantly diagnosed in women (75%; APA 2000a). There are particular problems in its diagnosis in adolescents and young adults where existential dilemmas may be mistakenly classified as BPD (DSM-IV). BPD commonly co-occurs with mood disorders, substance misuse, eating disorders, post-traumatic stress disorder (PTSD) and is also associated with other personality disorders (McGlashan 2000). Suicidal behaviour is reported to occur in up to 84% of patients with BPD (Soloff 2002), comorbid mood disorders or substance use being the most relevant risk factors for completion (Black 2004).

Although the short to medium-term outcome of BPD is poor - similar to that of schizophrenia - there is some evidence that long term follow-up shows a more favourable course, with remission rates of about 88% within ten years (Zanarini 2007). However, remission here only means that diagnostic criteria are not fulfilled and doesn't indicate the absence of any symptoms. Indeed, whereas acute symptoms such as self-mutilation, help-seeking suicide threats or attempts and impulsivity in most cases decrease with time, affective symptoms reflecting areas of chronic dysphoria, such as chronic feelings of emptiness, intense anger or profound abandonment largely remain (Zanarini 2007). Therefore, the majority of people with BPD still have significant levels of symptoms. Risk factors for a poorer long term outcome are comorbid substance use disorders, PTSD, and anxious cluster disorders (Zanarini 2005; Zanarini 2007), and also a family history of psychiatric disorder (especially mood disorders and substance use disorders), demographic issues, such as older age, longer treatment history, pathological childhood experiences, temperament issues, and adult psychosocial functioning (Zanarini 2007). It is estimated that about 60% to 78% of BPD patients make suicide attempts (Links 2009), but the rate of completed suicides is far less. Zanarini and colleagues found suicide rates of 4% during follow-up of ten years (Zanarini 2007), whereas Stone 1993 reported a suicide rate of 8.5% after 16.5 years. Study estimates of the lifetime risk of suicide among patients with BPD range from 3% to 10% (Links 2009).

The direct costs of BPD are considerable in that many people so affected make major demands on health professionals. The problem of deliberate self-harm is a particular issue in this group (Linehan 1997). In medical settings, people with BPD often present after self-harming behaviour or in suicidal crisis and are treated in emergency settings, often involving repeated psychiatric hospitaliza-

tions. Additionally, more than 80% of BPD patients are in individual psychotherapy for at least half of a six year period, and the same number is taking standing medication (Zanarini 2004a). Treatment settings and provisions for BPD patients may vary across different countries. Nevertheless, pharmacological interventions are increasingly being used to treat different facets of the BPD pathology spectrum, such as affective instability, impulsivity, dissociative states, or cognitive-perceptual symptoms. Associated pathology, such as depression, can likewise be the target of psychopharmacological interventions. Therefore, different classes of agents are used in the treatment of BPD patients, such as mood stabilisers, antipsychotics, or antidepressants (Lieb 2004).

In summary, BPD is a condition that has been extensively studied. It has a major impact on health facilities as those affected often present in crisis. Its long-term course leads to improvement but people continue to have considerable problems. The polythetic nature of the diagnosis is likely to lead to heterogeneity making it difficult to assess treatment efficacy.

OBJECTIVES

To evaluate the effects of pharmacological interventions in BPD.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised comparisons testing pharmacological interventions in BPD were included. Likewise, data from randomised cross-over studies up to the point of first cross-over (first period only) were eligible. We excluded outcomes of following periods since carry-over effects of the preceding treatments were likely. Furthermore, since BPD characteristically has no stable course but comprises rapid mood shifts, it seemed inappropriate for subjects to serve as their own controls (i.e. within-subject comparisons). Thus, we decided to use first period data only (Elbourne 2002).

At least 70% of study participants had to have a formal diagnosis of BPD. Studies including BPD patients as a subsample were included as well, if separate data on these patients were available. Studies were eligible if they stated both provider and recipient blinding. The adequacy of relevant arrangements was judged subsequently.

Types of participants

Adult patients with a formal diagnosis of BPD according to DSM criteria (see table below). Since its introduction in 1980, the criteria have only changed marginally.

DSM-III (APA 1980) **301.83 Borderline Personality Disorder**	**DSM-IV-TR** (APA 2000a) **301.83 Borderline Personality Disorder**
Diagnostic criterion A (5 of the following are required)	***Diagnostic criterion A: A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:***
(6) intolerance of being alone, e.g., frantic efforts to avoid being alone, depressed when alone	(1) frantic efforts to avoid real or imagined abandonment - note: do not include suicidal or self-mutilating behavior covered in criterion 5
(2) a pattern of unstable and intense interpersonal relationships, e.g., marked shifts of attitude, idealization, devaluation, manipulation (consistently using others for one's own ends)	(2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
(4) identity disturbance manifested by uncertainty about several issues relating to identity, such as self-image, gender identity, long-term goals or career choice, friendship patters, values, and loyalties, e.g., 'Who am I', 'I feel like I am my sister when I am good'	(3) identity disturbance: markedly and persistently unstable self-image or sense of self

(*Continued*)

(1) impulsivity or unpredictability in at least two areas that are potentially self-damaging, e.g., spending, sex, substance use, shoplifting, overeating, physically self-damaging acts	(4) impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating) - note: do not include suicidal or self-mutilating behavior covered in criterion 5
(7) physically self-damaging acts, e.g., suicidal gestures, self-mutilation, recurrent accidents or physical fights	(5) recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
(5) affective instability: marked shifts from normal mood to depression, irritability, or anxiety, usually lasting a few hours and only rarely more than a few days, with a return to normal mood	(6) affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, instability, or anxiety usually lasting a few hours and only rarely more than a few days)
(8) chronic feelings of emptiness or boredom	(7) chronic feelings of emptiness
(3) inappropriate, intense anger or lack of control of anger, e.g., frequent displays of temper, constant anger	(8) inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
	(9) transient, stress-related paranoid ideation or severe dissociate symptoms
Diagnostic criterion B: If under 18, does not meet the criteria for Identity Disorder	

Types of interventions

Any drug or a defined combination of drugs administered on a long-term basis (i.e. not only in case of crisis only) with the intention to treat BPD pathology.

Comparison treatments were classified in four categories:

- placebo;
- active comparator drug;
- combination of drugs;
- combined treatment, i.e. drug plus concomitant psychotherapeutic treatment or counselling.

Types of outcome measures

Outcomes could either be self-rated by patients or interviewer-assessed. Only adequately validated measures were included. Studies were only included if they provided data that could be used for effect size calculation for at least one of the primary or secondary outcomes defined below.

If a trial provided more than one measure for the same outcome construct (e.g. several questionnaires for the assessment of depression) the one most often used in the whole pool of included studies was used for effect size calculation, in order to minimise heterogeneity of outcomes in form and content. If a study reported the data of two assessment instruments that were equally frequently used, two reviewers (JS, BV) discussed the issue and chose the one which was in its content most appropriate for assessing BPD patients. Self-rated measures were preferred.

Primary outcomes

- Overall BPD severity.
- Severity of single BPD criteria according to DSM (avoidance of abandonment, dysfunctional interpersonal patterns, identity disturbance, impulsivity, suicidal ideation, suicidal behaviour, self-mutilating behaviour, affective instability, feelings of emptiness, anger, psychotic paranoid symptoms, dissociative symptoms).

Secondary outcomes

- Depression.
- Anxiety.
- General psychiatric pathology: comprehensive measures.

- Mental health status.
- Attrition.
- Adverse effects.

Search methods for identification of studies

Electronic searches

A qualified librarian searched the following electronic databases:

- CENTRAL (*The Cochrane Library*, 2009, issue 3);
- MEDLINE (January 1966 to 11 September 2009);
- CINAHL (1982 to September 2009);
- EMBASE (1980 to 37th week 2009);
- BIOSIS (1985 to 16 September 2009);
- PsycINFO (1872 to 2nd week September 2009);
- Sociological Abstracts (1963 to September 2009);
- ASSIA (1987 to June 2008);
- WEB OF SCIENCE (1981 to 12 September 2009);
- SIGLE (1980 to April 2006);
- COPAC (September 2009);
- Dissertation Abstracts (September 2009);
- ASSIA (1987 to September 2009).

For detailed search strategies and periods searched, see Appendix 1 to Appendix 13.

The following trial registers were searched via the WHO International Clinical Trials Registry Platform (ICTRP), using "borderline personality disorder" as search term:

- ISRCTN (International Standard Randomised Controlled Trial Number);
- ClinicalTrials.gov;
- ACTR (Australian Clinical Trials Registry).

Searching other resources

Relevant journals such as the Journal of Personality Disorders, the American Journal of Psychiatry, the Archives of General Psychiatry, the British Journal of Psychiatry and the Journal of Clinical Psychiatry were surveyed on a regular basis. Additionally, researchers in the field were contacted by e-mail and asked for unpublished data. Cross-references from relevant literature were also traced.

Data collection and analysis

Selection of studies

On the basis of publication abstracts, a first estimation of study eligibility was made. After that, the studies were critically appraised by two reviewers (JS, BV), independently, in order to decide about inclusion or exclusion of studies according to the above mentioned criteria. The RefMan bibliography management software was used in order to keep track of appraised trials and decisions. If the reviewers' judgements did not match, a third person (KL) was called upon to finally discuss inclusion or exclusion. To ensure transparency of study selection, flow charts were provided according to the QUOROM statement, showing how many hits had been excluded for a certain reason (Moher 1999).

Data extraction and management

Data were independently extracted by two reviewers (JS, BV). For this purpose, standardized data extraction forms were used, and data were double entered into the Review Manager software. If discrepancies arose that were not due to oversights, they were again resolved by discussion and adjudication by a third person (KL). In case of incomplete data reporting in publications, or where relevant subsample data were lacking, we contacted the study authors for more information.

Assessment of risk of bias in included studies

Again, two reviewers (JS, BV) independently rated the included trials in terms of their risk of bias. A standardized rating form was used in order to judge the probability of different risks of bias. Using The Cochrane Collaboration's tool for assessing risk of bias, the following questions were judged: Was the allocation sequence adequately generated? Was allocation adequately concealed? Was knowledge of the allocated intervention adequately prevented during the study (this question was judged separately for observer- and self-rated outcomes)? Were incomplete outcome data adequately addressed? Are reports of the study free of suggestion of selective outcome reporting? Was the study apparently free of other problems that could put it at a high risk of bias? Relevant text passages were quoted and, if necessary, commented upon. After that, the overall risk of bias was rated either as low (question answered 'Yes') or high (question answered 'No'). If insufficient detail was reported, or sufficient detail was known but the actual risk of bias was unknown, the judgement was 'Unclear'. Both reviewers (JS, BV) tried to reach a concerted estimation taking into account the information available. In case of disagreement, a third person (KL) was called in again.

Measures of treatment effect

Standardized mean differences (SMDs) were calculated on the basis of post-treatment results and follow-up data, respectively. Follow-up data were to be subsumed in 6 month steps. In case the direction of a scale was opposite to most of the other scales, the corresponding mean values were multiplied by -1 to ensure adjusted values.

For some trials, effect sizes could not be calculated as intended, i.e. as SMDs as described above, because relevant information was lacking. However, we decided to include these data by calculating

alternative estimates, and discussed the peculiar risk of over- or underestimating the effects.

The following effect sizes were used alternatively:

- Pre-standardized mean differences (MDs): The effects were calculated by using the post-treatment means as intended, but the standard deviations (SDs) of pre-treatment means. This may have led to an overestimation of effect sizes, as the pre-SDs are commonly smaller than post-SDs. This kind of effect size had to be used for the Goldberg 1986 outcome data.
- Standardised mean changes: The effects were calculated by using the pre-post mean change scores and their SDs. This is also a common method for preparing standardized effect sizes, but these data cannot be pooled with the common SMDs due to statistical assumptions (Higgins 2008). Standardized mean changes were calculated for Bogenschutz 2004; Schulz 2007 (partly) and Zanarini 2007 (partly).
- Mean change differences: For some outcomes of Schulz 2007 and Zanarini 2007, data allowed only for the calculation of the differences in mean baseline changes experienced by the two groups. Its standard errors (SE) were derived from the pair-wise P-values of the ANCOVA, as provided in the study reports. This is, therefore, a non-standardized measure reflecting the mere difference in reduction of assessment instrument scores. Both studies used the same assessment instrument.

Effect sizes were preferably calculated on the basis of intention-to-treat (ITT) data. If means and standard deviations from intention-to-treat analysis with missing values replaced were available, we used these data. In other cases we used analysis based on available data. Regarding dichotomous outcomes, the risk ratio (RR) was computed on an intention-to-treat basis. We acted on the conservative assumption that all participants who were lost to post-treatment assessment had an unfavourable outcome, e.g. they had left because the treatment had not been acceptable for them. We specified in the Characteristics of included studies risk of bias tables if continuous data of a certain study referred to the intention-to-treat or per-protocol sample.

All calculations were done using the latest release of the Review Manager software (RevMan 2008).

Unit of analysis issues

Cross-over trials

We planned to included data from randomised cross-over studies up to the point of first cross-over (first period only). We decided not to consider outcomes of following periods due to the likelihood of carry-over effects of the preceding treatment(s).

Repeated observations

We did not plan to combine repeated observations on participants in one meta-analysis. Data from different points of measurement (i.e. post-treatment, catamnestic data of 6-months-steps) were subject to separate analyses. Interim observations were not used.

Studies with multiple treatment groups

If a trial compared more than two intervention groups, all pair-wise comparisons were included as long as they were not subject to the same meta-analysis. If, for example, two different doses of a certain drug were tested against placebo, only the one comparison of placebo to the group with the dosage most similar to either recommended dosage standards or (if available) other trials testing this comparison was included. Thus, we avoided including the same group of participants twice in the same meta-analysis. If the experimental groups received different treatments with regard to contents, such as different drugs or combinations of drugs, and were not subject to the same meta-analysis, we included all comparisons.

Dealing with missing data

Where there was incomplete reporting of outcomes stated as having been assessed, we contacted the study authors. If data were not reported in an immediately usable way but required processing before being analysed, a statistician (GR) was consulted. Results derived from processed data were reported in sensitivity analyses.

Assessment of heterogeneity

Both visual inspection of the graphs and the I^2 statistics (Higgins 2003) were used to investigate statistical heterogeneity within a certain comparison. Besides the I^2 statistic, the number of studies and study characteristics such as duration, dose, and participants were taken into account to judge if heterogeneity was more probable due to clinical, i.e. explainable factors, or to unknown factors. In case of substantial heterogeneity, we made up subgroups, depending on study characteristics such as study size, duration, dose, or participants, and discussed the most apparent sources of heterogeneity.

Assessment of reporting biases

Funnel plots were to be provided for comparisons with sufficient primary studies. However, the poor numbers of study effects per comparison did not allow for constructing interpretable figures.

Data synthesis

If data pooling seemed feasible, the primary studies effects were pooled and their 95% confidence interval (CI) was calculated. A random-effects model was used, as some degree of clinical heterogeneity was present in most cases, though confined by study

inclusion criteria and not regarded as preventing from pooling in principle.

As a basic rule, I^2 scores of up to 75% were regarded as indicating possibly substantial, but accountable degrees of heterogeneity permitting statistical pooling. In case of I^2 scores exceeding 75%, we discussed if diversity of specific study characteristics (dose, duration, participants, outcome assessment, size) was likely to cause heterogeneity and tried to investigate this by setting up subgroups, the number of effect estimates permitting. If heterogeneity could not be explained, the estimates were not pooled.

Sensitivity analysis

Sensitivity analyses for the primary outcomes were planned to be performed as follows:

- trials requiring patients to have a certain psychiatric comorbidity in addition to BPD were to be excluded;
- only ITT data based outcomes were to be included.

Given the small numbers of effect estimates per comparison and outcome, we did not conduct sensitivity analyses, as this would only have led to omitting results. Instead, we strived to make all potential shortcomings of methodological quality explicit (see Characteristics of included studies tables and the "Risk of bias in included studies" section of the Description of studies) and to critically discuss all findings.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The study searches were re-run several times for updates. Due to overlaps in time periods covered and the use of sensitive search strategies (see Appendix 1 to Appendix 13), a large number of references was retrieved during preparation of this review. Study searches generated 13,972 references, 3723 of which were identified as duplicates. After screening of titles and abstracts of the remaining 10,249 hits, 489 citations merited closer inspection, and the full texts were ordered and scrutinized by two reviewers (JS, BV). Of these, 425 citations were excluded because they did not meet the inclusion criteria. Seven references referred to currently ongoing trials (see Characteristics of ongoing studies). A total of 57 different citations were included, relating to 28 RCTs.

Included studies

Setting of studies/study sample

Included studies were published between the years 1979 and 2009, with 20 of the 28 included trials dating from 2000 or later. The studies were conducted in either the USA (14 studies; Bogenschutz 2004; Frankenburg 2002; Goldberg 1986; Hollander 2001; Leone 1982; Linehan 2008; Reich 2009; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2003; Zanarini 2004) or in Western European countries (12 studies; 5 in Germany and/or Austria (Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Tritt 2005), two each in the UK (Montgomery 1979/82; Montgomery 81/82/83) and Spain (Pascual 2008; Soler 2005), and one each in Belgium (De la Fuente 1994), Ireland (Hallahan 2007) and the Netherlands (Rinne 2002)). There were two international multicentre trials: The Schulz 2007 trial was carried out in 39 study centres located in the USA and Western European countries. The RCT by Zanarini 2007 took place in 13 study centres in the USA, South America, and Eastern Europe.

Study samples ranged from N = 16 (Hollander 2001) to N = 314 (Schulz 2007) in size. In the Zanarini 2007 trial, even more patients had been involved altogether but there were three treatment groups, only two of which could be included in this meta-analysis, leaving 301 patients (see Characteristics of included studies. In total, the included studies provided data from 1742 patients.

Characteristics of participants

Demographic data

Most studies were not restricted to any gender, but nine studies included female patients only (Frankenburg 2002; Linehan 2008; Loew 2006; Rinne 2002; Simpson 2004; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004). The study of Nickel and colleagues reported the study data of a female (Nickel 2004) and a male sample (Nickel 2005) in separate publications. Patients were at least 18 years of age with the exception of two studies (Hallahan 2007; Nickel 2006) where participants had to be at least 16 years old. The mean participants' age ranged from 21.7 (Nickel 2006) to 38.6 (Hollander 2001) years, with 14 of the 28 studies having a mean age below 30 years.

Treatment settings

Study participants were mostly outpatients. The participants of only one trial were inpatients (De la Fuente 1994), while in two others participants were initially treated as inpatients for a minimum of two and three weeks, respectively (Soloff 1989; Soloff 1993), but could continue as outpatients afterwards.

Five trials dating from before 1990 diagnosed the participants according to DSM-III (Goldberg 1986; Leone 1982; Montgomery

1979/82; Montgomery 81/82/83; Leone 1982 Goldberg 1986 Soloff 1989), three studies used DSM-III-R criteria (De la Fuente 1994; Soloff 1993Salzman 1995; Soloff 1993). Diagnoses of all 20 remaining studies were based on DSM-IV or DSM-IV-TR.

Psychiatric comorbidity

Most study samples were clearly defined as BPD patients with a formal diagnosis of BPD as the main inclusion criterion (Bogenschutz 2004; De la Fuente 1994; Hollander 2001; Leone 1982; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Rinne 2002; Salzman 1995; Schulz 2007; Simpson 2004; Soler 2005; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007). However, there were a few exceptions: The Goldberg 1986 study required patients to have a diagnosis of BPD and/or schizotypal personality disorder (PD). Of the 50 patients included, 17 were diagnosed as having BPD, 13 as having schizotypal PD, and 20 as satisfying both sets of criteria. Hence, 74% of the study sample were BPD patients. The Montgomery 1979/82 and Montgomery 81/82/83 studies included patients admitted to a general hospital after a suicidal act, who had a history of two or more previous documented suicidal acts. BPD patients constituted 76.6% and 78.9%, respectively, of all included participants of the two studies. Similarly, all patients of the Hallahan 2007 trial were recruited from the accident and emergency department, where they had presented acutely with self-harm. Additionally, all had to to have a lifetime history of at least one other episode. Of all participants, 71% were diagnosed as having BPD. Only one trial required patients to satisfy another diagnosis besides BPD: All patients of the Frankenburg 2002 study additionally had a bipolar II disorder.

Exclusion criteria

Exclusion criteria varied between studies. Commonly, patients particularly prone to pharmacotoxic effects (i.e. pregnant or breastfeeding women, persons with known allergic reactions or intolerances) were excluded, as were patients with severe somatic illnesses, or neurological disorders (especially seizure disorders). Organic brain syndrome or mental retardation were also listed as exclusions by most studies.

The most common exclusion criteria relating to psychiatric conditions were schizophrenia, bipolar disorders, major depressive disorder and substance related disorders. Patients with any comorbid Axis-I disorder were excluded in two studies (De la Fuente 1994; Salzman 1995), as were patients with any unstable Axis-I disorder in another trial (Soler 2005).

In the remaining 25 trials, patients suffering from schizophrenia were excluded in 15 trials (Bogenschutz 2004; Goldberg 1986; Hallahan 2007; Hollander 2001; Linehan 2008; Loew 2006; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2004; Nickel 2005; Nickel 2006; Pascual 2008; Reich 2009; Schulz 2007; Tritt 2005). Another nine trials specified that even the lifetime diagnosis of schizophrenia was an exclusion criterion (Frankenburg 2002; Reich 2009; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007). Eight studies also excluded patients with current (Bogenschutz 2004; Linehan 2008) or lifetime schizoaffective disorder (Frankenburg 2002; Soloff 1993; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007).

Patients with the diagnosis of any bipolar disorder were excluded in 20 of all 28 included trials. However, Hallahan 2007; Leone 1982; Loew 2006; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2006 and Rinne 2002 did not exclude bipolar patients. Additionally, all patients of the Frankenburg 2002 study sample had a bipolar II disorder as an inclusion criterion (here, patients with bipolar I disorder were excluded). In the Soler 2005 trial, bipolar patients could be included if they were in a stable condition.

Patients with current major depressive disorder were not allowed in the majority of trials (besides the De la Fuente 1994 and Salzman 1995 trials that excluded any Axis-I disorder, and Soler 2005 that excluded any unstable Axis-I disorder): Bogenschutz 2004; Frankenburg 2002; Hollander 2001; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2004; Nickel 2005; Pascual 2008; Schulz 2007; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2003; Zanarini 2004; Zanarini 2007). The Goldberg 1986 trial excluded patients with melancholia, and Linehan 2008 excluded patients currently suffering from major depressive disorder with psychotic features.

Another frequent exclusion criterion was substance related disorder. Besides the two aforementioned trials that did not include patients with any Axis-I disorder (De la Fuente 1994; Salzman 1995), and the one trial that excluded patients with any unstable Axis-I condition (Soler 2005), there were ten trials (Bogenschutz 2004; Goldberg 1986; Hallahan 2007; Linehan 2008; Pascual 2008; Reich 2009; Schulz 2007; Simpson 2004; Soloff 1993; Zanarini 2007) that did not include patients who currently satisfied criteria for alcohol or drug dependence. Another eight trials did not even include patients abusing alcohol or drugs at the time of recruitment (Frankenburg 2002; Hollander 2001; Loew 2006; Nickel 2004; Nickel 2005; Tritt 2005; Zanarini 2001; Zanarini 2007). Therefore, only seven of the 28 trials did not state any substance related disorder as hindering patients from entering the trial (Leone 1982; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2006; Rinne 2002; Soloff 1989; Zanarini 2003).

Current suicidality was an explicit exclusion criterion in 13 trials (Bogenschutz 2004; Frankenburg 2002; Hollander 2001; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Salzman 1995; Tritt 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007). Eleven trials did not explicitly specify suicidality as an exclusion criterion (De la Fuente 1994; Goldberg 1986; Leone 1982; Pascual 2008; Reich 2009; Rinne 2002; Schulz 2007; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2003). How-

ever, all patients of the Montgomery 1979/82 and Montgomery 81/82/83 trials were recruited following admittance to hospital due to a suicidal act, so these patients can be assumed to have been acutely suicidal when entering the trial.

Severity of illness at baseline

The study participants' baseline severity of illness varied between studies. Seven studies used the Global Assessment scale (GAS; Endicott 1976) to assess individuals' level of functioning, and seven used the Global Assessment of Functioning scale (GAF; APA 1994). Both are 100-point single item rating scales used to rate functioning; on a hypothetical continuum from intact mental health to mental illness. The scale values range from 1, which represents the hypothetically most impaired individual, to 100, the hypothetically healthiest individual (APA 2000b). The GAS and GAF scores ranged from 42.2 to 72.4 and were, therefore, typical for psychiatric outpatients (APA 2000b). The average functioning in one study (Salzman 1995) was located at the lower end of the interval range or 71 to 80 ("slight impairment in functioning"), while the average level of functioning of the Goldberg 1986 study participants was rated between 61 and 70 ("some mild symptoms"). The participants of most studies (De la Fuente 1994; Hollander 2001; Frankenburg 2002; Reich 2009; Schulz 2007; Zanarini 2003; Zanarini 2004; Zanarini 2007) were located in the interval range from 51 to 60, defined as "having moderate symptoms or generally functioning with some difficulty". The samples of four other studies (Linehan 2008; Simpson 2004; Soloff 1989; Soloff 1993) had a lower level of functioning and were rated between 41 and 50, i.e. as having "any serious symptomatology or impairment in functioning that most clinicians would think obviously requires treatment or attention".

The Clinical Global Impressions Severity of Illness Scale (CGI-S; Guy 1976) was used in two trials to estimate participants' severity of illness. This scale covers seven items from 1 "not ill at all" to 7 "among the most extremely ill". Here, the average ratings ranged from 4.2 to 5.14. The average CGI-S ratings of Bogenschutz 2004 (4.3) was closest to item 4, "moderately ill", while the participants of the Soler 2005 trial were rated with an average of 5.14, which fits best with item 5, "markedly ill". A similar estimation was found by Pascual 2008, who used the Clinical Global Impressions Borderline Peronsality Disorder (CGI-BPD) scale specifically referring to the rating of BPD severity (Perez 2007). These patients had an average CGI-BPD severity of illness of 4.8.

Rinne 2002 provided data specifically concerning BPD severity of illness. On average, the participants met 6.95 (SD = 1.3) DSM BPD criteria. Additionally, the BPDSI (Borderline Personality Disorder Severity Index; Arntz 2003) was used to assess BPD severity. The BPDSI is a fully structured interview measuring the frequency of occurrence of all DSM-IV BPD criteria during the last three months. Each of the nine DSM criteria is operationalized as a subscale, and the sum of all subscales constitutes the BPDSI-total, with a possible range of 0 (no occurrence) to 90 (most severe). A BPDSI total score above 15 signifies BPD pathology (Arntz 2003). For inclusion, a BPDSI total score of 20 was required, and the average baseline mean of all participants was 32.9 (SD = 7.7), indicating moderate severity.

For the samples of the Loew 2006 and Nickel 2006 trials, the t-transformed baseline SCL-90-R global severity index scores (SCL-90-R-GSI) were reported. The SCL-90-R scale is a measure of the status of psychopathology along nine symptom constructs: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic-anxiety, paranoid ideation, and psychoticism. The GSI is essentially a mean of all scores. With t-transformed baseline GSI scores above 70 (Loew 2006: mean GSI at baseline 72.25; Nickel 2006: mean GSI at baseline: 74.7), the participants of these trials can be considered as having "high to very high mental stress" (Franke 2002). For the participants of the Hallahan 2007 trial it is reported that the 'mean scores for all psychometric instruments [i.e. concerning depression, impulsivity, perceived stress] were well in excess of published normative data'.

Concerning the trials of Nickel 2004; Nickel 2005; Tritt 2005; and Zanarini 2001, there were no psychometric data available relating to the overall severity of illness, psychopathologic burden or impairment. All samples were described as "moderately ill", and treatment histories were given (Nickel 2004: 10.3% had previously been hospitalized for psychiatric reasons, 58.6% had a history of psychotherapeutic treatment, and 69.0% had received pharmacotherapeutic treatment previously; Nickel 2005: 7.1% had previously been hospitalized for psychiatric reasons, 23.8% had been in psychotherapeutic treatment, and 57.1% had received pharmacotherapeutic treatment; Tritt 2005: 18.5% had previously been hospitalized for psychiatric reasons, 44.4% had been in psychotherapeutic treatment, and 71.1% had received pharmacotherapeutic treatment; Zanarini 2001: 14.3% had previously been hospitalized for psychiatric reasons, 82.1% had been in psychotherapeutic treatment, and 64.3% had received pharmacotherapeutic treatment). Treatment use may depend on availability and health care system specifics, though. However, all three trials excluded patients with bipolar disorders, substance-related disorders, schizophrenia, and especially acutely suicidal patients.

No psychometric data concerning the patients' severity of illness were available concerning the Montgomery 1979/82 and Montgomery 81/82/83 studies. However, all participants were included after admission to hospital following a suicidal act, and had a history of at least two more documented suicidal acts. Therefore, the severity of illness can be considered very serious.

Concerning the Leone 1982 trial sample, the only information available was that participants had to meet four or more of the diagnostic BPD characteristics described by Gunderson and Kolb, and two of these had to be rated as severe, two as at least moderate. Therefore, patients with rather lower levels of pathology may have been included.

Interventions

Comparisons

Older studies focused mainly on first-generational antipsychotics and antidepressants. Since the mid 1990s, second-generation antipsychotics, mood stabilisers, and selective serotonin reuptake inhibitor (SSRI) antidepressants have gained more attention.

The majority of studies involved two comparison groups. However, there were some studies with three comparison groups: Soloff 1989 tested two active groups, i.e. haloperidol and amitriptyline, against placebo, and Soloff 1993 tested haloperidol and phenelzine sulfate against placebo. Zanarini 2004 compared two active drugs in three different combinations, i.e. fluoxetine alone versus olanzapine alone versus fluoxetine plus olanzapine. Therefore, each of the three comparison groups was involved twice within this review. The different testings belonged to different comparison categories, and were therefore not pooled.

Additionally, Zanarini 2007 also compared three conditions, i.e. olanzapine in two different dosages, to placebo. Since the comparison of each of the two olanzapine groups to placebo would have belonged to the same comparison category, and would have led to pooling dependent data, we decided to include only one of the two olanzapine groups. Therefore, we chose the one olanzapine group with the dosage most closely matching the remaining olanzapine versus placebo comparisons.

In total, included studies comprised the following comparisons.

Active drug versus placebo

1. First-generation antipsychotics: thiothixene (Goldberg 1986), flupenthixol decanoate (Montgomery 1979/82), haloperidol (Soloff 1989; Soloff 1993).
2. Second-generation antipsychotics: aripiprazole (Nickel 2006), olanzapine (Bogenschutz 2004; Linehan 2008; Schulz 2007; Soler 2005; Zanarini 2001; Zanarini 2007), ziprasidone (Pascual 2008).
3. Mood stabilisers: carbamazepine (De la Fuente 1994), valproate semisodium (Frankenburg 2002; Hollander 2001), lamotrigine (Reich 2009; Tritt 2005), topiramate (Loew 2006; Nickel 2004; Nickel 2005).
4. Antidepressants: amitriptyline (Soloff 1989), fluoxetine (Salzman 1995; Simpson 2004), fluvoxamine (Rinne 2002), phenelzine sulfate (Soloff 1993), mianserin (Montgomery 81/82/83).
5. Miscellaneous: omega-3 fatty acids (Hallahan 2007; Zanarini 2003).

Active drug versus active comparator drug

1. First-generation antipsychotic versus first-generation antipsychotic: loxapine versus chlorpromazine (Leone 1982).
2. First-generation antipsychotic versus antidepressant: haloperidol versus amitriptyline (Soloff 1989), haloperidol versus phenelzine sulfate (Soloff 1993).
3. Second-generation antipsychotic versus antidepressant: olanzapine versus fluoxetine (Zanarini 2004).

Active drug versus combination of drugs

1. Second-generation antipsychotic versus second-generation antipsychotic plus antidepressant: olanzapine versus olanzapine plus fluoxetine (Zanarini 2004).
2. Antidepressant versus antidepressant plus second-generation antipsychotic: fluoxetine versus fluoxetine plus olanzapine (Zanarini 2004).

Study duration

The intervention times ranged from 32 days to 24 weeks, with a mean duration of 84.0 days (SD = 43.6), i.e. approximately 12 weeks.

Concomitant medication

In 13 of the 28 studies, patients were not taking any concomitant psychotropic medication (Bogenschutz 2004; Frankenburg 2002; Goldberg 1986; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Rinne 2002; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004). Four studies did not specify whether psychotropic medication was allowed or not (Hollander 2001; Linehan 2008; Montgomery 1979/82; Montgomery 81/82/83). Two trials gave no details on permissible drug treatment, but there was a washout period for tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) in one (De la Fuente 1994) and a one week placebo run-in, probably without any other psychotropic treatment, in the other (Salzman 1995). Some studies specified permissible drugs that could be taken in order to manage adverse effects, or to address certain symptoms that were not addressed by the study drugs. Mostly, these were drugs with sedative or anxiolytic effects.

In the Leone 1982 study, nighttime sedatives (flurazepam and chloral hydrate) could be taken. In the case of insomnia, participants of the Simpson 2004 study were allowed to take 50 to 100 mg/day of Trazodone. In cases of extrapyramidal reactions, participants of the Soloff 1989 study could take 2 mg/day of biperiden hydrochloride. Patients of both the Pascual 2008 and Soler 2005 studies could continue treatment with benzodiazepines, antidepressants or mood stabilisers, if initiated prior to study inclusion, but doses could not be modified. Participants of the Reich 2009 study were allowed to take one antidepressant but had to have been on a stable dose for at least one month. Patients of the Schulz 2007

and the Zanarini 2007 trials were allowed to take benzodiazepines and hypnotics.

Concomitant psychotherapeutic treatment

Concerning the permission of concomitant psychotherapy, six studies gave no details at all on this (Goldberg 1986; Hollander 2001; Leone 1982; Schulz 2007; Zanarini 2001; Zanarini 2003). In eight trials, psychotherapeutic treatment was an exclusion criterion (Hallahan 2007; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Rinne 2002; Tritt 2005). Although not cited as a reason for exclusion in two trials, no participants of the Frankenburg 2002 and Zanarini 2004 studies received psychotherapy at the time. In two further studies, very few patients received concomitant psychotherapy (Salzman 1995: two out of 22; Zanarini 2007: 10 out of 415). The Bogenschutz 2004 trial allowed patients to continue psychotherapeutic treatment if initiated more than three months prior to randomization, but there was no specification as to how many subjects actually did. Four trials provided supportive non-specific psychotherapeutic treatment to all their participants (De la Fuente 1994: "supportive atheoretical psychotherapy"; Montgomery 1979/82 and Montgomery 81/82/83: follow-up with support from social workers, community nurses and a crisis intervention team after admission due to a suicidal act; Pascual 2008: weekly two hour, non-specific group psychotherapy). There were three trials (Linehan 2008; Simpson 2004; Soler 2005) in which all participants received specific psychotherapeutic treatment, i.e. Dialectic Behavioural Therapy. All patients of the Soloff 1989 and Soloff 1993 studies started as inpatients for three and two weeks, respectively, but it was not specified whether they received psychotherapeutic treatment during this time and thereafter.

Outcome measures

As a rule, higher scores indicate more severe pathology. There are only two exceptions: GAF and GAS scores (mental health status assessments) are oppositely directed, i.e. higher scores indicate higher or better levels of functioning.

Some trials reported several measures relating to the same outcome, as defined for this review (e.g. for depression there were both Beck Depression Inventory (BDI) and Hamilton Depression Scale (HAM-D) scores available). To avoid an unnecessary inflation of type-I error, only one relevant result out of each study was used for effect size calculation. BPD-specific assessment instruments were first choice for primary outcome assessment. If none was available, the measure most often used in the whole pool of included studies was chosen for effect size calculation, in order to minimise the heterogeneity of outcomes in form and content. If there was no difference in the frequency of use, we chose the measure that we thought was in its contents most adequately reflecting the particular outcome in BPD patients. Self-rated measures were also preferred.

Concerning adverse events, objective data were preferred (i.e. weight increase in kg was used instead of the ratio of patients with perceived weight gain). The ratios of patients experiencing a certain adverse event in each group were only statistically compared if the event occurred more than once in at least one of the two groups. Table 1 (FGAs versus placebo), Table 2; Table 3 and Table 4 (SGAs versus placebo), Table 5; Table 6; and Table 7 (mood stabilisers versus placebos), Table 8 and Table 9 (antidepressants versus placebo), Table 10 (miscellaneous active agents versus placebo); Table 11 (FGAs versus FGAs); Table 12 (FGAs versus antidepressants); Table 13 (SGAs versus antidepressants); Table 14 (SGAs versus SGA+antidepressant) and Table 15 (antidepressants versus antidepressant+SGA) specify the measures the effect sizes were calculated from for each comparison category. If there were several measures available for the same outcome, the reasons for choosing a particular one were indicated.

Table 1. First-generation antipsychotics vs. placebo: outcome scales

	Haloperidol		**Flupenthixol decanoate**	**Thiothixene**
	Soloff 1989	**Soloff 1993**	**Montgomery 1979/82**	**Goldberg 1986**
BPD severity	-	BSI	-	SIB-borderline score
avoidance of abandonment	-	-	-	-
interpersonal problems	SCL-90-INT	ADS-rejection sensitivity	-	HSCL-INT
identity disturbance	-	-	-	-

Table 1. First-generation antipsychotics vs. placebo: outcome scales (*Continued*)

impulsivity	BIS, Ward Scale of Impulse Action Patterns, STIC BIS used because of width of use and self-reporting format	BIS, Ward Scale of Impulse Action Patterns, STIC BIS used because of width of use and self-reporting format	-	-
suicidal ideation	-	-	-	-
suicidal behaviour	-	-	number of patients with suicidal act during treatment (6 months period)	-
self-mutilating behaviour	-	-	-	-
affective instability	-	-	-	-
feelings of emptiness	-	-	-	-
anger	SCL-90-HOS, BDHI SCL-90-HOS used because of greater sensitivity to change	SCL-90-HOS, BDHI, ADS-reactivity SCL-90-HOS used because of greater sensitivity to change than BDHI and greater width of than ADS scale	-	HSCL-HOS
psychotic/paranoid symptoms	SCL-90-PAR,SCL-90-PSY, SSI SCL-90-PAR used because regarded as most adequately reflecting BPD relevant pathology	SCL-90-PAR, SCL-90-PSY, SSI SCL-90-PAR used because regarded as most adequately reflecting BPD relevant pathology	-	SIB-suspicious/paranoid subscale, HSCL-90-PSY SIB-suspicious/paranoid subscale used because regarded as most adequately reflecting BPD-relevant pathology
dissociative symptoms	-	-	-	
depression	BDI, SCL-90-DEP, Ham-D BDI used because of width of use and self-report format	BDI, SCL-90-DEP, Ham-D, ADS total BDI used because of width of use and self-report format	-	HSCL-DEP
anxiety	SCL-90-ANX	SCL-90-ANX	-	-
general psychiatric pathology	SCL-90-GSI	SCL-90-GSI	-	-

Table 1. First-generation antipsychotics vs. placebo: outcome scales (*Continued*)

mental health status	GAS	GAS	-	GAS
attrition	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation
adverse events	-	ADS-weight gain	-	-

Table 2. Second-generation antipsychotics vs. placebo: outcome scales (part 1)

	Aripiprazole	**Ziprasidone**
	Nickel 2006	**Pascual 2008**
BPD severity	-	CGI-BPD-global
avoidance of abandonment	-	CGI-BPD-abandonment
interpersonal problems	SCL-90-R-INT (t-transformed)	CGI-BPD-unstable relations
identity disturbance	-	CGI-BPD-identity
impulsivity	STAXI-OUT	CGI-BPD-impulsivity
suicidal ideation	-	CGI-BPD-suicide
self-mutilating behaviour	number of patients with self-injury during treatment (8 weeks period)	-
affective instability	-	CGI-BPD-affect instability
feelings of emptiness	-	CGI-BPD-emptiness
anger	SCL-90-R-HOS (t-transformed), STAXI-trait, STAXI-state, STAXI-anger in SCL-90-R-HOS used because regarded as most comprehensive measure	CGI-BPD-anger
psychotic/paranoid symptoms	SCL-90-R-PAR, SCL-90-R-PSY SCL-90-R-PAR used because considered as most adequately reflecting BPD relevant pathology	CGI-BPD-paranoid ideation; BPRS CGI-BPD used because specific for assessment in BPD patients
dissociative symptoms	-	-
depression	Ham-D, SCL-90-R-DEP Ham-D used because also reported by other tri-	Ham-D-17; BDI Ham-D used because also reported by other tri-

Table 2. Second-generation antipsychotics vs. placebo: outcome scales (part 1) (*Continued*)

	als within this comparison category	als within this comparison category
anxiety	HARS; SCL-90-R-ANX HARS used because also reported by other trials within this comparison category	HARS
general psychiatric pathology	SCL-90-R-GSI	SCL-90-R-GSI
adverse effects	-	attrition
patient reported adverse events	-	minor sedation, dizziness, uneasy feeling

Table 3. Second-generation antipsychotics vs. placebo: outcome scales (part 2)

	Olanzapine			
	Bogenschutz 2004	**Linehan 2007**	**Soler 2005**	**Zanarini 2001**
BPD severity	-	-	-	-
avoidance of abandonment	CGI-abandonment	-	-	-
interpersonal problems	CGI-unstable relationships, SCL-90-R-INT CGI-unstable relationships used because specific for assessment in BPD patients	-	-	-
identity disturbance	CGI-identity disturbance	-	-	-
impulsivitiy	CGI-impulsivity	-	Behavioural reports of numbers of episodes of impulsivity/aggressive behaviour	-
suicidal ideation	CGI-recurrent suicidal ideation	number of patients with high suicidality scores on OAS-M-suicidality subscale (i.e., reporting frequent suicide ideation and/or planning or behaviour)	-	-

Table 3. Second-generation antipsychotics vs. placebo: outcome scales (part 2) (*Continued*)

suicidal behaviour	-		Behavioural reports of numbers of episodes of self-injuring behaviour/ suicide attempts	-
self-mutilating behaviour	-	number of patients with self-injury during treatment	-	-
affective instability	CGI-affective instability	-	-	-
feelings of emptiness	CGI-chronic feelings of emptiness	-	-	-
anger	CGI-inappropriate anger, OAS-M, AIAQ, SCL-90-HOS CGI-inappropriate anger used because specific for assessment in BPD patients	-	-	-
psychotic/paranoid symptoms	CGI-transient paranoia or dissociation, SCL-90-PSY, SCL-90-PAR CGI-transient paranoia or dissociation used because specific for assessment in BPD patients	-	-	-
depression	-	Ham-D	Ham-D	-
anxiety	-		HARS	-
general psychiatric pathology	-		-	-
mental health status	-		CGI-S	-
attrition	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation
adverse effects	baseline to endpoint weight change (kg)	baseline to endpoint weight change (kg)	baseline to endpoint weight change (kg) , baseline to endpoint increase in cholesterol levels (mg/dl)	baseline to endpoint weight change (kg)

Table 3. Second-generation antipsychotics vs. placebo: outcome scales (part 2) (*Continued*)

patient reported adverse events	-	-	-	constipation, sedation

Table 4. Second-generation antipsychotics vs. placebo: outcome scales (part 3)

	Olanzapine	
	Schulz 2007	**Zanarini 2007**
BPD severity	Zan-BPD-total	Zan-BPD-total
avoidance of abandonment	Zan-BPD-frantic efforts to avoid abandonment	Zan-BPD-frantic efforts to avoid abandonment
interpersonal problems	ZAN-BPD-unstable interpersonal relationships	ZAN-BPD-unstable interpersonal relationships, SCL-90-R-INT ZAN-BPD-unstable relationships used because specific for assessment in BPD patients
identity disturbance	ZAN-BPD-identity disturbance	ZAN-BPD-identity disturbance
impulsivity	ZAN-BPD-impulsivity that are self-damaging, OAS-M-aggression ZAN-BPD-impulsivity used because specific for assessment in BPD patients	ZAN-BPD-impulsivity that are self-damaging, OAS-M-aggression ZAN-BPD-impulsivity used because specific for assessment in BPD patients
suicidal ideation	ZAN-BPD-suicidal or self-mutilating behaviour	ZAN-BPD-suicidal or self-mutilating behaviour, OAS-M-suicidality ZAN-BPD subscale used because specific for assessment in BPD patients
suicidal behaviour	-	-
self-mutilating behaviour	-	-
affective instability	ZAN-BPD-affective instability	ZAN-BPD-affective instability
chronic feelings of emptiness	ZAN-BPD-chronic feelings of emptiness	ZAN-BPD-chronic feelings of emptiness
anger	ZAN-BPD-intense anger	ZAN-BPD-intense anger, OAS-M-irritability, SCL-90-R-HOS ZAN-BPD subscale used because specific for assessment in BPD patients
psychotic/paranoid symptoms	ZAN-BPD-paranoid ideation of dissociation	ZAN-BPD-paranoid ideation of dissociation, SCL-90-R-PAR ZAN-BPD subscale used because specific for assessment in BPD patients

Table 4. Second-generation antipsychotics vs. placebo: outcome scales (part 3) (*Continued*)

depression	MADRS	MADRS, SCL-90-R-DEP MADRS used because also available for Schulz 2007
anxiety	-	SCL-90-R-ANX
general psychiatric pathology	SCL-90-R-GSI	SCL-90-R-GSI
mental health status	GAF, Sheehan Scale GAF used because of width of use	GAF, Sheehan Scale GAF used because of width of use
attrition	number of patients lost after randomisation	number of patients lost after randomisation
adverse effects	baseline to endpoint weight change (kg)	baseline to endpoint weight change (kg)
patient-reported adverse events	anxiety, dry mouth, fatigue, headache, increased appetite, insomnia, nausea, number of patients experiencing any AE, sedation, somnolence all used	disturbed attention, dry mouth, fatigue, headache, increased appetite, insomnia, nausea, number of patients experiencing any AE, somnolence
laboratory values	lipids (baseline to endpoint mean changes): LDL cholesterol (mmol/L), total cholesterol (mmol/L) liver function values (baseline to endpoint mean changes): ALT/SGPT (U/L), AST/SGOT (U/L), total bilirubin (umol/L), direct bilirubin (umol/L) prolactin (micrograms/L)	lipids (baseline to endpoint mean changes): HDL cholesterol (mmol/L), total cholesterol (mmol/L), triglycerides fasting (mmol/L) liver function values (baseline to endpoint mean changes): GGT (GGPT/SGGT/YGGT; U/L), ALT/SGPT (U/L), AST/SGOT (U/L) prolactin baseline to endpoint mean change (micrograms/L) blood values (baseline to endpoint mean changes): leukocyte count (GI/L), monocytes (GI/L), neutrophils segmented (GI/L), platelet count (GI/L)

Table 5. Mood stabiliser vs. placebo: outcome scales (part 1)

	Carbamazepine	**Valproate Semisodium**	
	De la Fuente 1993	Frankenburg 2002	Hollander 2001
BPD severity	-	-	-
avoidance of abandonment	-	-	-
interpersonal problems	SCL-90-INT	SCL-90-INT	
identity disturbance	-	-	-

Table 5. Mood stabiliser vs. placebo: outcome scales (part 1) (*Continued*)

impulsivity	Acting-out Scale: number of patients worsened or unimproved as compared to baseline	MOAS	OAS-M-aggression (not used: Assault Questionnaire, because of close affinity of OAS-M with the MOAS scale as used by the Frankenburg trial
suicidal ideation	-	-	OAS-M-suicidality
suicidal behaviour	-	-	-
self-mutilating behaviour	-	-	-
affective instability	-	-	-
feelings of emptiness	-	-	-
anger	SCL-90-HOS	SCL-90-HOS	OAS-M-irritability
psychotic/parnoid symptoms	SCL-90-PAR (not used: BPRS as the SCL-scale had also been used by another trial within this comparison category; SCL-90-PSY as the PAR subscale reflects BPD relevant pathology more adequately)	-	-
dissociative symptoms	-	-	-
depression	SCL-90-DEP (not used: Ham-D as the SCL-90-DEP subscale was also available from other trials within this comparison category)	SCL-90-DEP	BDI
anxiety	SCL-90-ANX	-	-
general psychiatric pathology	SCL-90-total	-	-
mental health status	-	-	CGI-I: number of patients with an CGI-I of 3 or more (i.e., minimally improved to very much worse)
attrition	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation

Table 5. Mood stabiliser vs. placebo: outcome scales (part 1) (*Continued*)

adverse effects: weith gain	-	weight gain (kg; derived out of lb data)	-

Table 6. Mood stabilisers vs. placebo: outcome scales (part 2)

	Lamotrigine	
	Tritt 2005	Reich 2009
BPD severity	-	ZAN-BPD-total
avoidance of abandonment	-	-
interpersonal problems	-	-
identity disturbance	-	-
impulsivity	STAXI-anger out (not used: STAXI-anger in, STAXI-control)	ZAN-BPD-impulsivity
suicidal ideation	-	-
suicidal behaivour	-	-
self-mutilating behaviour	-	-
affective instability	-	ZAN-BPD-affective instability (not used: Affective Lability Scale)
feelings of emptiness	-	-
anger	STAXI-anger trait (not used: STAXI-anger state, as this subscale refers only to the intensity of angry feelings at the time of testing)	-
psychotic/paranoid sympotms	-	-
dissociative symptoms	-	-
depression	-	-
anxiety	-	-
general psychiatric pathology	-	-
mental health status	-	-

Table 6. Mood stabilisers vs. placebo: outcome scales (part 2) (*Continued*)

attrition	number of patients lost after randomisation	number of patients lost after randomisation
adverse effects: absolute weight	weight (kg)	-
patient-reported adverse events	-	number of patients with rash

Table 7. Mood stabilisers vs. placebo: outcome scales (part 3)

	Topiramate		
	Loew 2006	Nickel 2004	Nickel 2005
BPD severity	-	-	-
avoidance of abandonment	-	-	-
interpersonal problems	SCL-90-R-INT (t-transformed)	-	-
identity disturbance	-	-	-
impulsivity	-	STAXI-anger out (not used: STAXI-anger in, STAXI-control)	STAXI-anger out (not used: STAXI-anger in, STAXI-control)
suicidal ideation	-	-	-
suicidal behaivour	-	-	-
self-mutilating behaviour	-	-	-
affective instability	-	-	-
feelings of emptiness	-	-	-
anger	SCL-90-R-HOS (t-transformed)	STAXI-anger trait (not used: STAXI-anger state, as this subscale refers only to the intensity of angry feelings at the time of testing)	STAXI-anger trait (not used: STAXI-anger state, as this subscale refers only to the intensity of angry feelings at the time of testing)
psychotic/paranoid sympotms	SCL-90-R-PAR (t-transformed) (not used: SCL-90-R-PSY, as the SCL-90-R-PAR subscale reflects BPD relevant pathology more adequately)		

Table 7. Mood stabilisers vs. placebo: outcome scales (part 3) (*Continued*)

dissociative symptoms	-	-	-
depression	SCL-90-R-DEP (t-tranformed)	-	-
anxiety	SCL-90-R-ANX (t-tranformed)	-	-
general psychiatric pathology	SCL-90-R-GSI (t-transformed)	-	-
mental health status	-	-	-
attrition	number of patients lost after randomisation	number of patients lost after randomisation	number of patients lost after randomisation
adverse effects: absolute weight	weight (kg)	weight (kg)	weight (kg)
patient-reported adverse events	memory problems, troubles in concentrating, headache, fatigue, dizziness, menstrual pain, paresthesia	-	-

Table 8. Antidepressants vs. placebo: outcome scales (part 1)

	Amitriptyline	**Fluoxetine**	
	Soloff 1989	Salzman 1995	Simpson 2004
BPD severity	-	-	-
avoidance of abandonment	-	-	-
interpersonal problems	SCL-90-INT	-	-
identity disturbance	-	-	-
impulsivity	BIS; not used: Ward Scale of Impulsive Action, Self-Report Test of Impulse Control total because BIS is a self-report measure and broadly used	-	OAS-M-aggression; not used: STAXI-anger-out because other OAS-M-subscales were also used for several outcomes (s. below)
suicidal ideation	-	-	OAS-M-suicidality
suicidal behaviour	-	-	-

Table 8. Antidepressants vs. placebo: outcome scales (part 1) (*Continued*)

self-mutilating behaviour	-	-	OAS-M-assault against self
affective instability			
feelings of emptiness	-	-	-
anger	SCL-90-HOS not used: BDHI, ADDS-reactivity)	POMS-anger; not used: OAS-M-anger against objects (only one spectrum of anger entailed), PDRS-anger (only based on one interviewer-rated item)	-
psychotic/paranoid symptoms	SCL-90-PAR (not used: SCL-90-PSY, IMPS, SSI because SCL-90-PAR is a self-rated measure most adequately reflecting BPD relevant pathology	-	-
dissociative symptoms	-	-	DES
depression	BDI; not used: SCL-90-DEP, Ham-D-17, Ham-D-24, ADS, as all but the SCL-90-DEP scale are observer rated, and the BDI is more commonly used in the assessment of depression than the SCL-90-DEP	Ham-D; not used: POMS-dep because the Ham-D was also used by other studies within this comparison category	BDI
anxiety	SCL-90-ANX	-	STAI
general psychiatric pathology	SCL-90-GSI	-	-
mental health status	GAS	GAS	GAF
attrition	number of non-completers	-	number of non-completers
adverse effects	-	-	-

Table 9. Antidepressants vs. placebo: outcome scales (part 2)

	SSRI: Fluvoxamine	**MAOI: Phenelzine**	**Mianserin**
	Rinne 2002	Soloff 1993	Montgomery 81/82/83
BPD severity	-	BSI	-

Table 9. Antidepressants vs. placebo: outcome scales (part 2) (*Continued*)

avoidance of abandonment	-	-	-
dysfunctional interpersonal patterns	-	ADI-rejection sensitivity	-
identity disturbance	-	-	-
impulsivity	BPDSI-impulsivity	BIS; not used: Ward Scale of Impulsive Action, Self-Report Test of Impulse Control total because BIS is a self-report measure and broadly used	-
suicidal ideation	-	-	-
suicidal behaviour	-	-	-
self-mutilating behaviour	-	-	number of patients with self-harming behaviour during 6 months of treatment
affective instability	BPDSI-rapid mood shifts	-	-
feelings of emptiness	-	-	-
anger	BPDSI-anger	SCL-90-HOS; not used: BDHI, ADDS-reactivity)	-
psychotic/paranoid ideation	-	SCL-90-PAR; not used: SCL-90-PSY, IMPS, SSI because SCL-90-PAR is a self-rated measure most adequately reflecting BPD relevant pathology	-
dissociative symptoms	-	-	-
depression	-	BDI; not used: SCL-90-DEP, Ham-D-17, Ham-D-24, ADS, as all but the SCL-90-DEP scale are observer rated, and the BDI is more commonly used in the assessment of depression than the SCL-90-DEP	-
anxiety	-	SCL-90-ANX	-
general psychiatric pathology	-	SCL-90-GSI	-

Table 9. Antidepressants vs. placebo: outcome scales (part 2) (*Continued*)

mental health status	-	GAS	-
attrition	number of patients not completing the study protocol	number of patients not completing the study protocol	-
adverse effects	-	ADI-weight gain	

Table 10. Miscellaneous active agents vs. placebo: outcome scales

	Omega-3 fatty acid	
	Hallahan 2007	**Zanarini 2003**
BPD severity	-	-
avoidance of abandonment	-	-
interpersonal problems	-	-
identity disturbance	-	-
impulsivity	-	MOAS
suicidal ideation	OAS-M-suicidality: number of patients with suicidality subscale score >1 (i.e., at least slight suicidal tendency)	-
suicidal behaviour	-	-
self-mutilating behaviour	number of patients with self-harm episodes during treatment	-
affective instability	-	-
feelings of emptiness	-	-
anger	-	-
psychotic/paranoid symptoms	-	-
dissociative symptoms	-	-
depression	number of patients not experiencing at least a 50% or 70% reduction of depressive pathology as assessed both by BDI and HAM-D BDI used as it shows high concurrent valid-	MADRS

Table 10. Miscellaneous active agents vs. placebo: outcome scales (*Continued*)

	ity with MADRS, whereas HAM-D mainly focusses on somatic depressive symptoms 50% cut-off data used as this is more sensitive to change, as are the continuous data reported by the other relevant trial in this comparison category	
anxiety	-	-
general psychiatric pathology	-	-
mental health status	-	-
attrition	number of patients lost after randomisation	number of patients lost after randomisation
adverse effects	-	-

Table 11. First-generation antipsychotic vs. first generation antipsychotic: outcome scales

	Loxapine vs. Chlorpromazine
	Leone 1982
BPD severity	-
avoidance of abandonment	-
interpersonal problems	-
identity disturbance	-
impulsivity	-
suicidal ideation	-
suicidal behaviour	-
self-mutilating behaviour	-
affective instability	-
feelings of emptiness	-
anger	-
psychotic/paranoid symptoms	-

Table 11. First-generation antipsychotic vs. first generation antipsychotic: outcome scales (*Continued*)

dissociative symptoms	-
depression	-
anxiety	-
general psychiatric pathology	-
mental health status	-
attrition	number of patients lost after randomisation
patient-reported adverse events	number of patients experiencing any AE, sleepiness/drowsiness, restlessness, muscle spasms, fainting spells

Table 12. First-generation antipsychotics vs. antidepressants: outcome scales

	Haloperidol vs. Amitriptyline	**Haloperidol vs. Phenelzine Sulfate**
	Soloff 1989	**Soloff 1993**
BPD severity	-	BSI
avoidance of abandonment	-	-
interpersonal problems	SCL-90-INT	ADS-rejection sensitivity
identity disturbance	-	-
impulsivity	BIS, Ward Scale of Impulse Action Patterns, STIC BIS used because of width of use and self-reporting format	BIS, Ward Scale of Impulse Action Patterns, STIC BIS used because of width of use and self-reporting format
suicidal ideation	-	-
suicidal behaviour	-	-
self-mutilating behaviour	-	-
affective instability	-	-
feelings of emptiness	-	-

Table 12. First-generation antipsychotics vs. antidepressants: outcome scales (*Continued*)

anger	SCL-90-HOS, BDHI SCL-90-HOS used because of greater sensitivity to change	SCL-90-HOS, BDHI, ADS-reactivity SCL-90-HOS used because of greater sensitivity to change than BDHI and greater width of than ADS scale
psychotic/paranoid symptoms	SCL-90-PAR,SCL-90-PSY, SSI SCL-90-PAR used because regarded as most adequately reflecting BPD relevant pathology	SCL-90-PAR, SCL-90-PSY, SSI SCL-90-PAR used because regarded as most adequately reflecting BPD relevant pathology
dissociative symptoms	-	-
depression	BDI, SCL-90-DEP, Ham-D BDI used because of width of use and self-report format	BDI, SCL-90-DEP, Ham-D, ADS total BDI used because of width of use and self-report format
anxiety	SCL-90-ANX	SCL-90-ANX
general psychiatric pathology	SCL-90-GSI	SCL-90-GSI
mental health status	GAS	GAS
attrition	number of patients lost after randomisation	number of patients lost after randomisation
adverse events	-	ADS-weight gain

Table 13. Second-generation antipsychotics vs. antidepressants: outcome scales

	Olanzapine vs. Fluoxetine
	Zanarini 2004
BPD severity	-
avoidance of abandonment	-
interpersonal problems	-
identity disturbance	-
impulsivity	OAS-M
suicidal ideation	-
suicidal behaviour	-
self-mutilating behaviour	-

Table 13. Second-generation antipsychotics vs. antidepressants: outcome scales (*Continued*)

affective instability	-
feelings of emptiness	-
anger	-
psychotic/paranoid symptoms	-
dissociative symptoms	-
depression	MADRS
anxiety	-
general psychiatric pathology	-
mental health status	-
attrition	number of patients lost after randomisation
Adverse effects	baseline to endpoint weight change (kg)
patient-reported adverse events	number of patients experiencing mild sedation, akathisia

Table 14. Second-generation antipsychotics vs. second-generation antipsychotics plus antidepressants: outcome scales

	Olanzapine vs. Olanzapine + Fluoxetine
	Zanarini 2004
BPD severity	-
avoidance of abandonment	-
interpersonal problems	-
identity disturbance	-
impulsivity	OAS-M
suicidal ideation	-
suicidal behaviour	-
self-mutilating behaviour	-

Table 14. Second-generation antipsychotics vs. second-generation antipsychotics plus antidepressants: outcome scales (*Continued*)

affective instability	-
feelings of emptiness	-
anger	-
psychotic/paranoid symptoms	-
dissociative symptoms	-
depression	MADRS
anxiety	-
general psychiatric pathology	-
mental health status	-
attrition	number of patients lost after randomisation
Adverse effects	baseline to endpoint weight change (kg)
patient-reported adverse events	number of patients experiencing mild sedation, akathisia

Table 15. Antidepressants vs. antidepressants plus second-generation antipsychotics: outcome scales

	Fluoxetine vs. Fluoxetine + Olanzapine
	Zanarini 2004
BPD severity	-
avoidance of abandonment	-
interpersonal problems	-
identity disturbance	-
impulsivity	OAS-M
suicidal ideation	-
suicidal behaviour	-
self-mutilating behaviour	-

Table 15. Antidepressants vs. antidepressants plus second-generation antipsychotics: outcome scales (*Continued*)

affective instability	-
feelings of emptiness	-
anger	-
psychotic/paranoid symptoms	-
dissociative symptoms	-
depression	MADRS
anxiety	-
general psychiatric pathology	-
mental health status	-
attrition	number of patients lost after randomisation
Adverse effects	baseline to endpoint weight change (kg)
patient-reported adverse events	number of patients experiencing mild sedation, akathisia

In the following, a survey of the assessment instruments finally used in the review is given. Measures used in the included studies to assess outcomes that were not relevant to this review are not considered, as are data that were of relevance but could not be used for effect size calculation due to the format of reporting.

Primary outcomes

(1) BPD severity

(a) Borderline Syndrome Index (BSI): Soloff 1993.
(b) Clinical Global Impression (CGI) scale for use in borderline personality disorder patients (CGI-BPD), global: Pascual 2008.
(c) Schedule of Interviewing Schizotypal Personalities (SIB), subscale "borderline score": Goldberg 1986.
(d) Zanarini Rating Scale for borderline personality disorder (Zan-BPD) total score: Schulz 2007; Reich 2009; Zanarini 2007.

(2) Avoidance of abandonment

(a) CGI-BPD, subscale "abandonment": Bogenschutz 2004; Pascual 2008.
(b) ZAN-BPD, subscale "frantic efforts to avoid abandonment": Schulz 2007; Zanarini 2007.

(3) Interpersonal problems

(a) Atypical Depression Inventory, subscale "rejection sensitivity": Soloff 1993.
(b) CGI-BPD, subscale "unstable relationships": Bogenschutz 2004; Pascual 2008.
(c) Hopkins Symptom Checklist (HSCL), Symptom Checklist-90 (SCL-90) or Symptom Checklist-90-Revised (SCL-90-R), subscale "interpersonal sensitivity": De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Loew 2006; Nickel 2006; Soloff 1989; Zanarini 2001.
(d) ZAN-BPD, subscale "unstable interpersonal relationships": Schulz 2007; Zanarini 2007.

(4) Identity disturbance

(a) CGI-BPD, subscale "identity disturbance": Bogenschutz 2004; Pascual 2008.
(b) ZAN-BPD, subscale "identity disturbance": Schulz 2007; Zanarini 2007.

(5) Impulsivity

(a) Acting out-Scale, ratio of patients with status quo or worsened after treatment: De la Fuente 1994.
(b) Barrett Impulsiveness Scale (BIS): Soloff 1989; Soloff 1993.
(c) Behavioural reports of numbers of episodes of impulsivity/aggressive behaviour: Soler 2005.
(d) Borderline Personality Disorder Severity Index (BPDSI), subscale "impulsivity": Rinne 2002.
(e) CGI-BPD, subscale "impulsivity": Bogenschutz 2004; Pascual 2008.
(f) Modified Overt Aggression Scale (MOAS), total score: Frankenburg 2002; Zanarini 2003.
(g) Overt Aggression Scale-Modified (OAS-M), subscale "aggression": Hollander 2001; Simpson 2004.
(h) Stait-Trait Anger Expression Inventory (STAXI), subscale "anger out": Nickel 2004 and Nickel 2005; Nickel 2006; Tritt 2005.
(i) ZAN-BPD, subscale "impulsivity that are self-damaging": Reich 2009; Schulz 2007; Zanarini 2007.

(6) Suicidal behaviour/suicidal ideation

(a) Behavioural reports of numbers of episodes of self-injuring behaviour/suicide attempts: Soler 2005.
(b) CGI-BPD, subscale "recurrent suicidal ideation": Bogenschutz 2004; Pascual 2008.
(c) OAS-M, subscale "suicidality": Hallahan 2007; Hollander 2001; Simpson 2004.
(d) OAS-M, subscale "suicidality": number of patients with high suicidality, i.e. frequent suicide ideation and/or planning or behaviour: Linehan 2008.
(e) Ratio of patients with suicidal act during treatment: Montgomery 1979/82; Montgomery 81/82/83.
(f) ZAN-BPD, subscale "suicidal or self-mutilating behaviour": Schulz 2007; Zanarini 2007.

(7) Self-injurious behaviour

(a) Ratio of patients with self-injury during treatment period: Hallahan 2007; Linehan 2008; Nickel 2006.
(b) OAS-M, subscale "auto aggression": Simpson 2004.

(8) Affective instability

(a) BPDSI, subscale "rapid mood shifts": Rinne 2002.
(b) CGI-BPD, subscale "affective instability": Bogenschutz 2004; Pascual 2008.
(c) ZAN-BPD, subscale "affective instability": Reich 2009; Schulz 2007; Zanarini 2007.

(9) Chronic feelings of emptiness

(a) CGI-BPD, subscale "chronic feelings of emptiness": Bogenschutz 2004; Pascual 2008.
(b) ZAN-BPD, subscale "chronic feelings of emptiness": Schulz 2007; Zanarini 2007.

(10) Inappropriate anger

(a) BPDSI, subscale "anger": Rinne 2002.
(b) CGI-BPD, subscale "inappropriate anger": Bogenschutz 2004; Pascual 2008.
(c) HSCL, SCL-90 or SCL-90-R, subscale "hostility": De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Loew 2006; Nickel 2006; Soloff 1989; Soloff 1993; Zanarini 2001.
(d) OAS-M, subscale "irritability": Hollander 2001.
(e) Profile of Mood States (POMS), subscale "anger": Salzman 1995.
(f) STAXI, subscale "trait anger": Nickel 2004 and Nickel 2005; Tritt 2005.
(g) ZAN-BPD, subscale "intense anger": Schulz 2007; Zanarini 2007.

(11) Psychotic/paranoid symptoms or dissociation

(a) CGI-BPD, subscale "transient paranoia or dissociation": Bogenschutz 2004; Pascual 2008.
(b) Dissociative Experiences Scale (DES): Simpson 2004.
(c) HSCL, SCL-90 or SCL-90-R, subscale "paranoid ideation": De la Fuente 1994; Loew 2006; Nickel 2006; Soloff 1989; Soloff 1993.
(d) SIB, subscale "suspicious/paranoid": Goldberg 1986.
(e) ZAN-BPD, subscale "paranoid ideation of dissociation": Schulz 2007; Zanarini 2007.

Secondary outcomes

(1) Depression

(a) BDI: Hallahan 2007; Hollander 2001; Simpson 2004; Soloff 1989; Soloff 1993.

(b) HAM-D: Linehan 2008; Nickel 2006; Pascual 2008; Salzman 1995; Soler 2005.
(c) HSCL, SCL-90 or SCL-90-R, subscale "depression": De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Loew 2006.
(d) Montgomery-Asberg Depression Rating Scale (MADRS): Schulz 2007; Zanarini 2003; Zanarini 2004; Zanarini 2007.

(2) Anxiety

(a) Hamilton Anxiety Rating Scale (HARS): Nickel 2006; Pascual 2008; Soler 2005.
(b) HSCL, SCL-90 or SCL-90-R, subscale "anxiety": De la Fuente 1994; Loew 2006; Soloff 1989; Soloff 1993; Zanarini 2007.
(c) State-Trait Anxiety Inventory (STAI), trait score: Simpson 2004.

(3) General psychiatric pathology

(a) HSCL, SCL-90 or SCL-90-R, Global Severity Index (GSI): De la Fuente 1994; Nickel 2006; Loew 2006; Pascual 2008; Schulz 2007; Soloff 1989; Soloff 1993; Zanarini 2001; Zanarini 2007.

(4) Mental health status

(a) Clinical Global Impressions Scale (CGI), subscale "severity of illness": Soler 2005.
(b) Global Assessment Scale (GAS): De la Fuente 1994; Goldberg 1986; Salzman 1995; Soloff 1989; Soloff 1993.
(c) Global Assessment of Functioning (GAF): Schulz 2007; Simpson 2004; Zanarini 2007.
(d) Ratio of patients with Clinical Global Impressions Scale - improvement (CGI-I) score of 3 or more (i.e. minimally improved to very much worse): Hollander 2001.

(5) Attrition

(a) Ratio of patients lost after randomisation in each group: De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Hallahan 2007; Hollander 2001; Leone 1982; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Pascual 2008; Reich 2009; Rinne 2002; Schulz 2007; Simpson 2004; Soler 2005; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004; Zanarini 2007.

(6) Adverse events - body weight change

(a) Total weight at endpoint (kg): Loew 2006; Nickel 2004; Nickel 2005; Tritt 2005.
(b) Baseline to endpoint weight change (kg): Bogenschutz 2004; Frankenburg 2002; Linehan 2008; Schulz 2007; Soler 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007.
(c) Atypical Depression Inventory (ADS), subscale "weight gain": Soloff 1993.

(7) Patient-reported adverse events (AE)

(a) Any AE: Leone 1982; Pascual 2008; Schulz 2007; Zanarini 2007.
(b) Akathisia: Zanarini 2004.
(c) Anxiety: Schulz 2007.
(d) Constipation: Zanarini 2001.
(e) Disturbed attention: Zanarini 2007.
(f) Dizziness: Loew 2006.
(g) Dry mouth: Schulz 2007; Zanarini 2007.
(h) Fainting spells: Leone 1982.
(i) Fatigue: Loew 2006; Schulz 2007; Zanarini 2007.
(j) Headache: Loew 2006; Schulz 2007; Zanarini 2007.
(k) Increased appetite: Schulz 2007; Zanarini 2007.
(l) Insomnia: Schulz 2007; Zanarini 2007.
(m) Memory problems: Loew 2006.
(n) Menstrual pain: Loew 2006.
(o) Muscle spasms: Leone 1982.
(p) Nausea: Schulz 2007; Zanarini 2007.
(q) Paraesthesia: Loew 2006.
(r) Restlessness: Leone 1982.
(s) Sedation: Schulz 2007; Zanarini 2001; Zanarini 2004.
(t) Sleepiness/drowsiness: Leone 1982.
(u) Somnolence: Schulz 2007; Zanarini 2007.
(v) Trouble in concentrating: Loew 2006.

(8) Laboratory values

(a) Lipids: High-density lipoprotein (HDL) cholesterol baseline to endpoint mean change (mmol/L): Zanarini 2007.
(b) Lipids: Low-densitiy lipoprotein (LDL) cholesterol baseline to endpoint mean change (mmol/L): Schulz 2007.
(c) Lipids: total cholesterol baseline to endpoint mean change (mmol/L): Schulz 2007; Zanarini 2007.
(d) Lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L): Zanarini 2007.
(e) Liver function: gamma-glutamyl transferase (GGT) baseline to endpoint mean change Units per litre (U/L): Zanarini 2007.
(f) Liver function: Alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT) baseline to endpoint mean change (U/L): Schulz 2007; Zanarini 2007.
(g) Liver function: Aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT) baseline to endpoint mean change (U/L): Schulz 2007; Zanarini 2007.

(h) Liver function: total bilirubin baseline to endpoint mean change (μmol/L): Schulz 2007.
(i) Liver function: direct bilirubin baseline to endpoint mean change (μmol/L): Schulz 2007.
(j) Prolactin: baseline to endpoint mean change (μg/L): Schulz 2007; Zanarini 2007.
(k) Blood values: leukocyte count baseline to endpoint mean change (GI/L): Zanarini 2007.
(l) Blood values: monocytes baseline to endpoint mean change (GI/L): Zanarini 2007.
(m) Blood values: neutrophils, segmented, baseline to endpoint mean change (GI/L): Zanarini 2007.
(n) Blood values: platelet count baseline to endpoint mean change (GI/L): Zanarini 2007.

Risk of bias in included studies

The assessment of the risk of bias caused several problems, mainly because about one third of trials dated from before publication of the CONSORT statement, and may, therefore, have paid less attention to reporting all relevant issues. However, we tried to be consistent in judging methodological quality throughout all included trials, old or not, which may have resulted in a more 'liberal' judgment.
The judgments for each single study can be found in the Characteristics of included studies tables, and are summarised in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

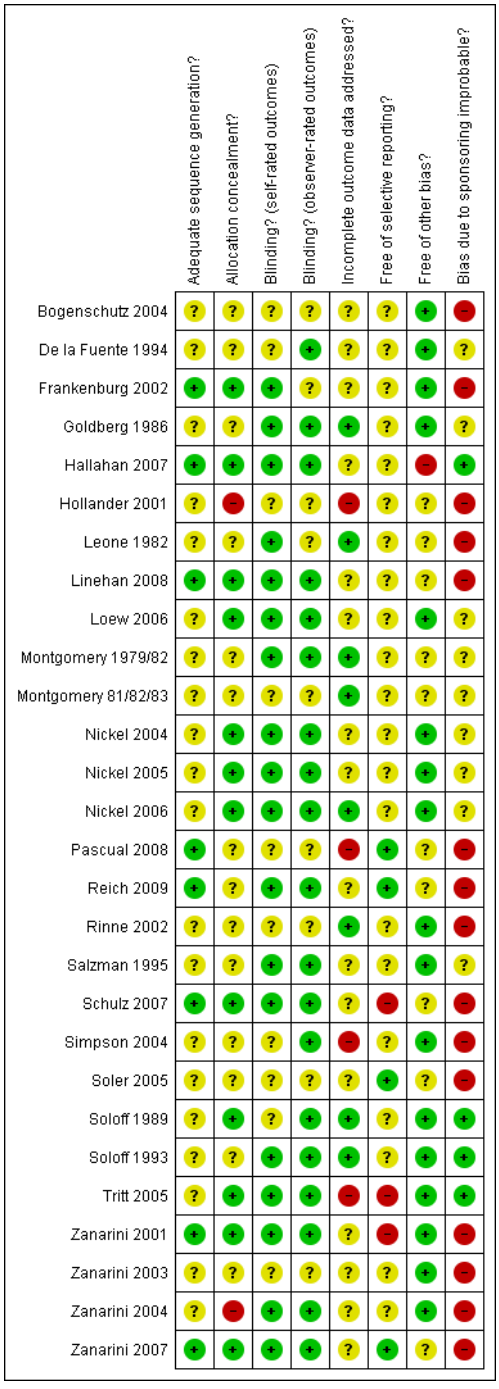
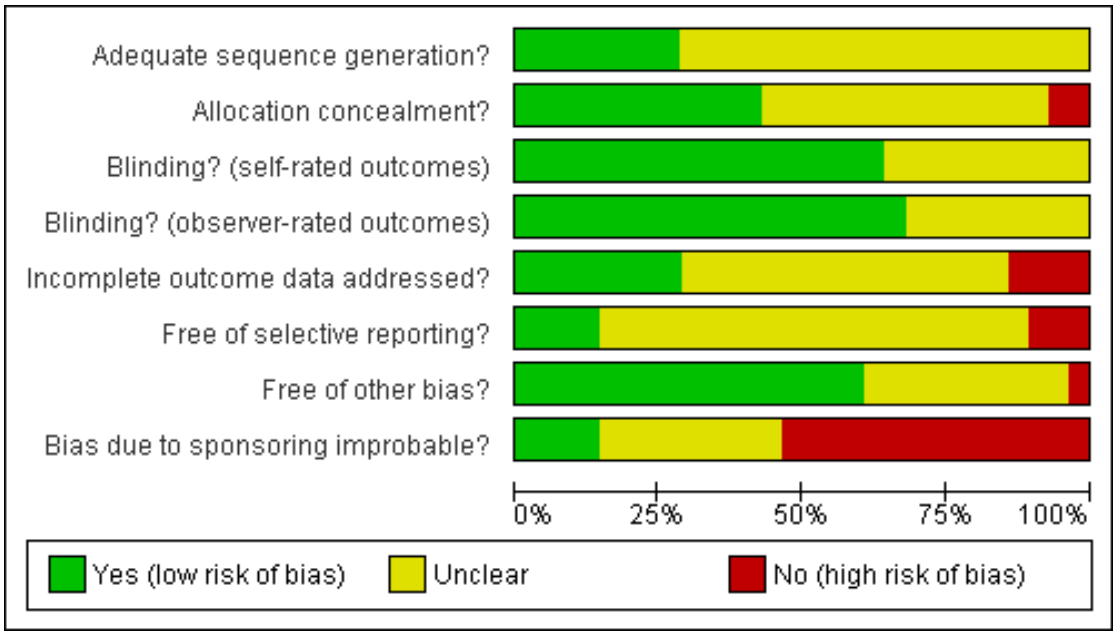


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

All included trials stated treatment allocation as "randomised". Some trials (Frankenburg 2002; Hallahan 2007; Linehan 2008; Reich 2009; Zanarini 2001) reported the use of a randomised number sequence. Participants of the Simpson 2004 trial were randomised "blocked on the presence of a diagnosis of major depressive disorder or post-traumatic stress disorder (PTSD)", which seems justifiable in the light of an overall small sample size. In the Pascual 2008 trial, allocation was carried out "in blocks of four generated using the SPSS software". The Schulz 2007 and Zanarini 2007 trials were both carried out in parallel multicentre studies by sponsorship of EliLilly and Company. The publications only make mention of the use of a randomisation code. However, as one of the reviewers (KL) had been involved at one of the study centres, we know that randomisation was carried out centrally, and investigators were strictly kept blinded to the patients' allocation. These trials were rated 'Yes' with regard to adequacy of sequence generation.

Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006 and Tritt 2005 specified that randomisation had been performed confidentially by the clinic administration, but there were no further details of how this was actually done. Leone 1982 stated that "subjects [...] were selected randomly", but in the light of the identical numbers of men and women in the two groups, the use of some matching procedure seems probable. All remaining trials were only described as having used a randomisation procedure, without giving further details. Thus, it remains unclear if sequence generation was adequate or not.

The actual concealment of allocation was judged adequate for twelve trials where relevant details were given, such as involvement of a third, independent person to disperse medication or to adjust dosages (especially in case of agents with very peculiar adverse effects that could disclose treatment allocation to the clinician) or the use of numbered tablet boxes (Frankenburg 2002; Hallahan 2007; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Schulz 2007; Soloff 1989; Tritt 2005; Zanarini 2001; Zanarini 2007). In the Zanarini 2004 trial, the actual numbers of participants in each group were not concordant with the intended group sizes (45 participants should be allocated "in equal numbers" to three groups, but the group sizes differed in an irreproducible way). Hollander 2001 stated that "although the planned patient assignment ratio was 2:1 [...], the

ratio was actually 3:1". Here, allocation seems not to have been conducted adequately. For the remaining 14 trials, no information was given how adequate allocation concealment was ensured, but there were also no indications for inadequate concealment (Bogenschutz 2004; De la Fuente 1994; Goldberg 1986; Leone 1982; Montgomery 1979/82; Montgomery 81/82/83; Pascual 2008; Reich 2009; Rinne 2002; Salzman 1995; Simpson 2004; Soler 2005; Soloff 1993; Zanarini 2003).

Blinding

Self-rated outcomes

All trials were stated as "double-blind" by their authors. In cases where details were given to assure that patients were kept blind, e.g. by using opaque capsules, blinding was judged as adequate. The majority of trials either did so, or there was no risk of bias since there were no self-rated outcomes assessed (Bogenschutz 2004; Frankenburg 2002; Goldberg 1986; Hallahan 2007; Leone 1982; Linehan 2008; Loew 2006; Montgomery 1979/82; Nickel 2004; Nickel 2005; Nickel 2006; Reich 2009; Salzman 1995; Schulz 2007; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007). The remaining nine trials gave no details, but there were also no indications for non-blindness of participants (e.g. by possibly experiencing very peculiar adverse effects, or by joining the same therapy groups as other participants; Bogenschutz 2004; De la Fuente 1994; Hollander 2001; Montgomery 81/82/83; Pascual 2008; Rinne 2002; Simpson 2004; Soler 2005; Soloff 1989; Zanarini 2003).

Blinding of outcome assessors

The majority of trials reported that outcome observers were blinded or did not use observer-rated outcomes, so the risk of bias was rated as improbable in this regard (De la Fuente 1994; Goldberg 1986; Hallahan 2007; Hollander 2001; Linehan 2008; Loew 2006; Nickel 2004; Nickel 2005; Reich 2009; Salzman 1995; Schulz 2007; Simpson 2004; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2004; Zanarini 2007). For the remaining trials, it was not apparent if the person who actually assessed outcomes was blinded, and the risk of bias was judged unclear (Bogenschutz 2004; Frankenburg 2002; Leone 1982; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2006; Pascual 2008; Rinne 2002; Soler 2005; Zanarini 2003).

Incomplete outcome data

Incomplete outcome data were rated as adequately handled for the trials of Goldberg 1986; Leone 1982; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2006; Rinne 2002; Soloff 1989; Soloff 1993. In these cases, only data referring to the intention-to-treat (ITT) sample were used. Mostly, a last-observation-carried-forward (LOCF) approach was used in primary studies. This item was also judged 'Yes' if the primary study reported on completers only but drop-outs could be imputed ex post as having the negative outcome for the purpose of this review.

The risk of bias due to inadequate handling of incomplete outcome data was judged 'unclear' for studies that used a LOCF approach but had a total drop-out of more than 20% of the initial sample (Bogenschutz 2004; Frankenburg 2002; Hallahan 2007; Linehan 2008; Soler 2005; Zanarini 2001; Zanarini 2007). Two trials used a LOCF approach, but it was not clear how the trial participants were chosen out of eligible subjects (Loew 2006; Tritt 2005). For another three trials it was not clear if continuous data referred to the ITT or completer samples (De la Fuente 1994; Reich 2009; Schulz 2007). The risk of bias due to incomplete outcome data was therefore judged 'unclear'. The item was also judged 'unclear' for studies that reported on completers only, but the overall drop-out rate did not exceed 10%, and reasons for dropping out were specified, not related to treatments and balanced across groups. This was the case for Nickel 2004; Nickel 2005; Salzman 1995; Zanarini 2003; Zanarini 2004.

One trial that both had high drop-out rates (i.e. more than 10%) and excluded non-completers from analyses were judged 'No', i.e. as having a high risk of bias due to incomplete outcome data (Simpson 2004). Two trials with very high attrition rates (i.e. more than 50%) plus unclear selection of study participants out of eligible patients were judged 'No' as well (Hollander 2001; Pascual 2008).

Selective reporting

For the majority of cases no study protocols were available, so there was not enough information to judge if selective reporting was present or not. These trials were rated as 'Unclear' in terms of being biased due to selective reporting (Bogenschutz 2004; De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Hallahan 2007; Hollander 2001; Leone 1982; Linehan 2008; Loew 2006; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2004; Nickel 2005; Nickel 2006; Rinne 2002; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993; Zanarini 2003; Zanarini 2004). Four studies that protocols were available for with no major differences of final reporting to the pre-specified way were judged 'Yes', i.e. as having a low risk of bias with this regard (Pascual 2008; Reich 2009; Soler 2005; Zanarini 2007). In one case reported outcomes and the study protocol differed (Schulz 2007), for another study the authors said they only reported significant findings (Zanarini 2001), and a third one provided data from one assessment instrument only, but it seems implausible that in such a complex trial only one assessment instrument had been used (Tritt 2005). These three trials were rated 'No'.

Other potential sources of bias

Carry-over effects from previous pharmacological treatment

To avoid carry-over effects from additional psychotropic medication, concomitant psychotropic treatment was not allowed during the experimental treatment, and, in the main part, a washout-phase or placebo run-in preceded the experimental phase. Internal validity was judged as not threatened by concomitant medication for the trials of Bogenschutz 2004; De la Fuente 1994; Frankenburg 2002; Goldberg 1986; Loew 2006; Nickel 2004; Nickel 2005; Nickel 2006; Rinne 2002; Salzman 1995; Simpson 2004; Soloff 1989; Soloff 1993; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004.

The risk of bias due to co-medication was judged unclear for 10 studies because of the following reasons: no details were given whether concomitant psychotropic drug use was allowed or not, or if there was a drug washout (Hollander 2001; Linehan 2008; Montgomery 1979/82; Montgomery 81/82/83; Zanarini 2007); participants were allowed to continue previous psychotropic treatment if initiated prior to study participation (Pascual 2008; Reich 2009; Soler 2005); participants were allowed to take sedatives/hypnotics concomitantly (Leone 1982; Schulz 2007). For the case of Hallahan 2007, bias seemed to be probable, as concomitant medication was allowed without restrictions, and changes could also be made anytime.

Bias due to sponsoring

Two studies (Soloff 1989; Soloff 1993) declared financial support solely from national non-profit organisations. Another study (Tritt 2005) claimed that there was no funding at all. Hallahan 2007 explicitly declared that the active preparation and placebo were provided by a certain company, but that it was not otherwise involved in the study. These four trials were rated as having a low risk of bias due to sponsoring.

For six studies (Bogenschutz 2004; Frankenburg 2002; Leone 1982; Linehan 2008; Reich 2009; Zanarini 2004) the authors declared support by pharmaceutical companies, seven studies were supported in part by pharmaceutical companies (Hollander 2001; Pascual 2008; Rinne 2002; Simpson 2004; Soler 2005; Zanarini 2001; Zanarini 2003). Another two studies were sponsored by a pharmaceutical company, and the company's trial reports were used in this review (Schulz 2007; Zanarini 2007). These 15 studies were rated 'No' in terms of bias to sponsoring being unlikely.

No sufficient information about funding and sponsoring was available for the remaining nine studies (De la Fuente 1994; Goldberg 1986; Loew 2006; Montgomery 1979/82; Montgomery 81/82/83; Nickel 2004; Nickel 2005; Nickel 2006; Salzman 1995). These were rated 'unclear'.

In summary, 14 out of 28 included trials were at least partly supported by pharmaceutical companies, with no further specification of the companies' roles in conducting and evaluating. For these, bias due to sponsoring cannot be ruled out.

Effects of interventions

Generally, SMDs with a negative value indicate a greater reduction of pathology by the first treatment in line (mostly: verum treatment) in contrast to the alternate treatment (mostly: placebo). Should the opposite be the case, i.e. positive values favour the first mentioned treatment, this will be indicated.

Risk ratios (RRs) with a value lower than one indicate that the risk of a certain event in the first treatment (mostly: active agent) group is lower than that in the comparison treatment (mostly: placebo) group.

For a survey of all outcomes and assessment instruments, see the Description of studies/Outcome measures section. In addition, tables are provided showing per comparison which assessment instruments were used for assessment of the results that the final effect estimates are based upon, and in case several measures were available for a certain outcome, why the definite one was chosen (Table 1 to Table 10).

1. Drug versus placebo comparisons

For corresponding analyses of drug versus placebo comparisons, refer to Analysis 15.1 to Analysis 65.1.

Primary outcomes

1.1 BPD severity

There were two single study estimates for first-generation antipsychotics, one comparing haloperidol to placebo, the other one thiothixene. Both indicated less favourable results for the groups receiving first-generation antipsychotics (haloperidol: N = 58, 1 RCT, SMD 0.30, 95% confidence interval (CI) -0.22 to 0.82; thiothixene: N = 50, 1 RCT, SMD calculated on basis of post-means and pre-SD 0.28, 95% CI -0.28 to 0.83).

Two large RCTs assessed the impact of olanzapine treatment on BPD severity. The pooled SMDs, based on change scores, indicated olanzapine treated patients to be slightly better-off, but not significantly (N = 596, 2 RCTs, SMD calculated on basis of changes scores -0.15, 95% CI -0.41 to 0.10, I^2 = 60%). For ziprasidone, data also indicated better results for verum treated patients, but the effect was not significant (N = 60, 1 RCT, SMD -0.47, 95% CI -0.98 to 0.05).

Data for mood stabiliser treatment were provided by one RCT (N = 27) that tested lamotrigine. There was a non-significant effect estimate of moderate size (SMD calculated on basis of change scores -0.43, 95% CI -1.20 to 0.34).

For treatment with antidepressants, only one RCT provided data for BPD severity. Here, the group with phenelzine sulfate treatment had slightly better results, but the difference was, again, not significant (N = 62, 1 RCT, SMD -0.15, 95% CI -0.65 to 0.35).

In summary, none of the investigated agents (i.e. first- and second-generation antipsychotics, one MAOI antidepressant) yielded a significant effect on overall BPD severity.

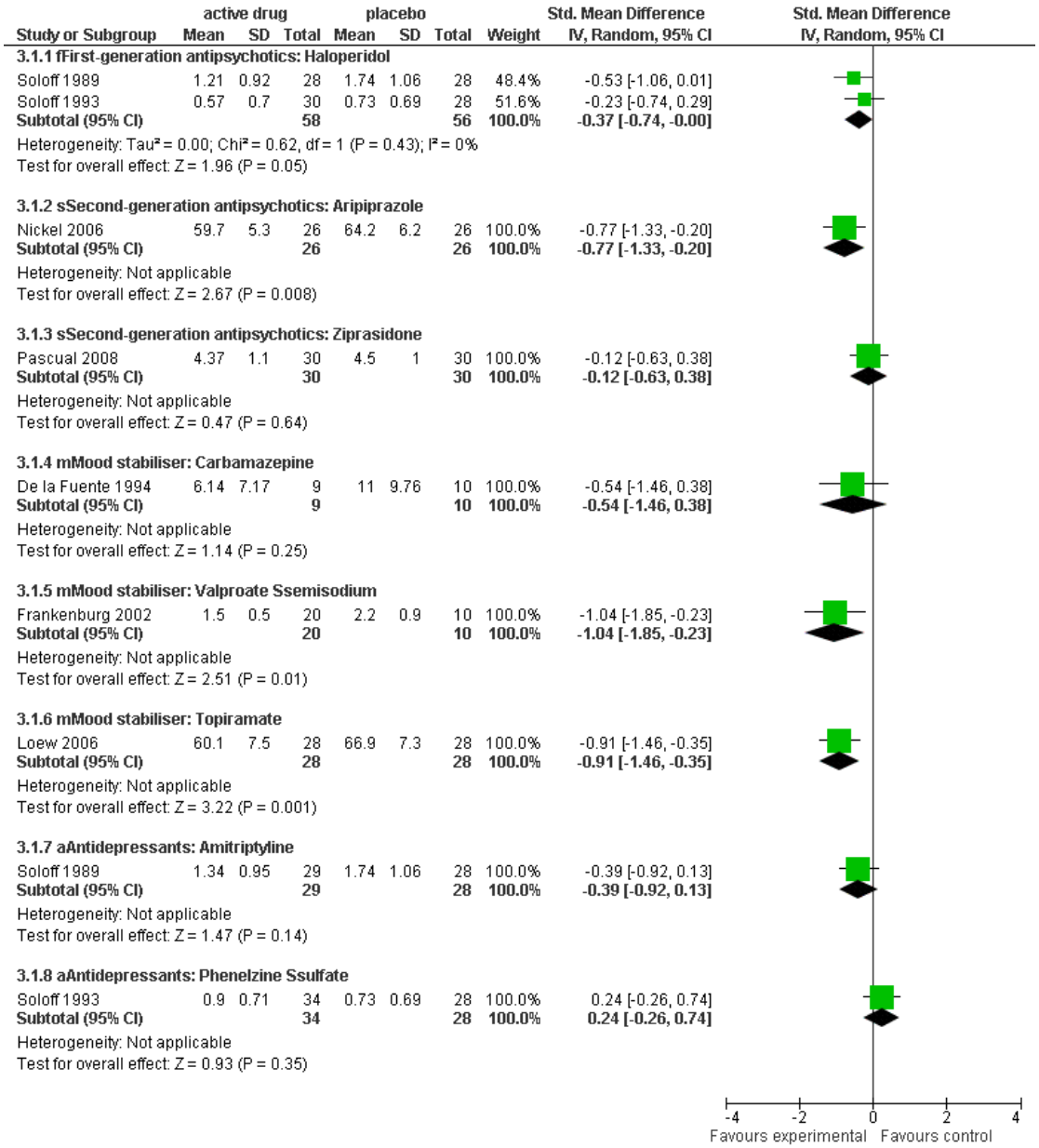
1.2 Avoidance of abandonment

Data were available for second-generation antipsychotics only. There was almost no difference between ziprasidone and placebo treated patients (N = 60, 1 RCT, SMD -0.08, 95% CI -0.58 to 0.43) and neither did data indicate a substantial impact for olanzapine treatment (N = 631, 3 RCTs, SMD calculated on basis of change scores -0.01, 95% CI -0.22 to 0.21, I^2 = 35%).
In summary, the data did not suggest substantial effects of second-generation antipsychotics for this outcome. The outcome was not assessed for any other agent.

1.3 Interpersonal problems

First- and second-generation antipsychotics, mood stabilisers and antidepressants were investigated with regard to possible amelioration of interpersonal problems (see Figure 3 for SMDs, and Analysis 3.2 to Analysis 3.4 for additional effect sizes).

Figure 3. Forest plot of comparison: 3.1.1 Active drug versus placebo: Interpersonal problems, SMDs



As can be seen, most estimates favoured drug treatment, with exception of phenelzine sulfate, for which less favourable results were reported. Significant effects were found for the second-generation antipsychotic aripiprazole (SMD -0.77, N = 52, 1 RCT, 95% CI -1.33 to -0.20) and the mood stabilisers valproate semisodium (SMD -1.04, N = 30, 1 RCT, 95% CI -1.85 to -0.23) and topiramate (SMD -0.91, N = 56, 1 RCT, 95% CI -1.46 to -0.35). All significant effects were derived from one single study each.

In summary, there were significant effects of medium to large size for aripiprazole, valproate semisodium, and topiramate, but all were based on single studies only.

1.4 Identity disturbance

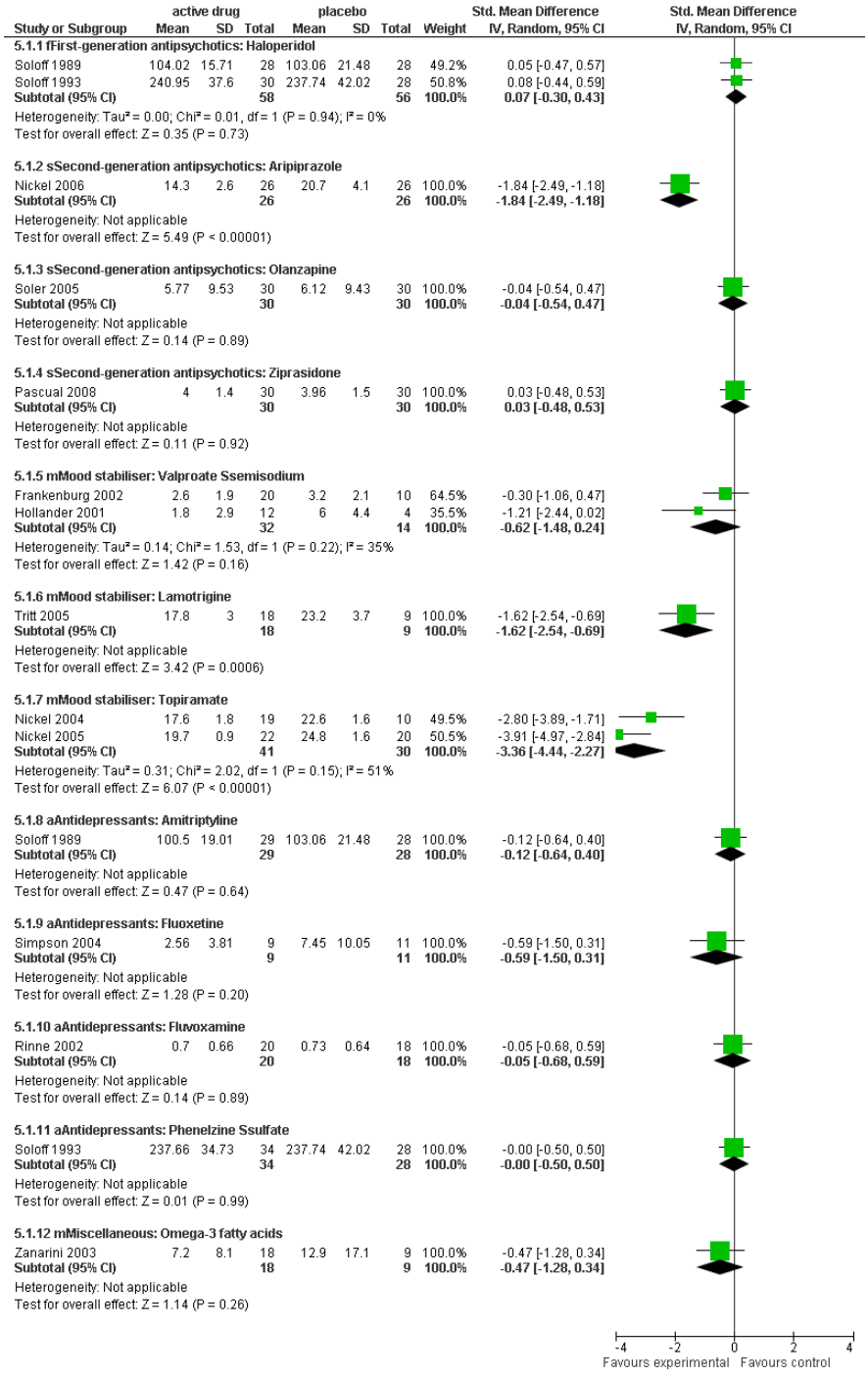
The pooled mean change SD for olanzapine was -0.06 (N = 631, 3 RCTs, 95% CI -0.21 to 0.10, I^2 = 0%). The single study estimate (SMD) for ziprasidone was -0.38 (N = 60, 1 RCT, 95% CI -0.90 to 0.13).

In summary, data for this outcome were only available for the second-generation antipsychotics olanzapine and ziprasidone, with no significant results.

1.5 Impulsivity

Impulsivity had been assessed in trials investigating first- and second-generation antipsychotics, mood stabilisers, antidepressants, and omega-3 fatty acids. SMDs are displayed in Figure 4, additional effect sizes were calculated for olanzapine and carbamazepine (see Analysis 5.2 to Analysis 5.4).

Figure 4. Forest plot of comparison: 5.1 Active drug versus placebo: Impulsivity, SMDs



Again, most findings were based on single study estimates. Large, significant effects were found for the second-generation antipsychotic aripiprazole (N = 52, 1 RCT, SMD -1.84, 95% CI -2.49 to -1.18), and the mood stabilisers lamotrigine (two RCTs the estimates of which could not be pooled: N = 27, 1 RCT, SMD -1.62, 95% CI -2.54 to -0.69; N = 27, 1 RCT, SMD on basis of baseline to post mean changes -1.41, 95% CI -2.27 to -0.55) and topiramate (N = 71, 2 RCTs, SMD -3.36, 95% CI -4.44 to -2.27, I^2 = 51%). Available data indicated no beneficial effects for the first-generation antipsychotic haloperidol, the second-generation antipsychotics olanzapine and ziprasidone, the mood stabiliser valproate semisodium, the antidepressants amitriptyline, fluoxetine, fluvoxamine, and phenelzine sulfate, or omega-3 fatty acids.

In summary, data consistently indicated significant beneficial effects for mood stabilisers, and the second-generation antipsychotic aripiprazole. The direction of study estimates indicates no beneficial effects for first-generation antipsychotics and antidepressants.

1.6 Suicidal ideation

Usable data concerning the effect of the second-generation antipsychotic olanzapine on suicidal ideation were provided by four RCTs (Bogenschutz 2004; Linehan 2008; Schulz 2007; Zanarini 2007). Due to different formats of data reporting, only two of these could be pooled, and several kinds of effect sizes had to be calculated. There was a small effect for one RCT in terms of mean change difference (N = 291, 1 RCT, MCD -0.10, 95% CI -0.20 to -0.00). However, the remaining three RCTs indicated more suicidal ideation in olanzapine treated patients, resulting in one non-significant effect (RR of having high suicidality scores 1.20, N = 24, 1 RCT, 95% CI 0.50 to 2.88), and even another significant one: the pooled mean change SD of the remaining two trials was 0.29 (N = 340, 2 RCTs, 95% CI 0.07 to 0.50, I^2 = 0%). For ziprasidone, another second-generation antipsychotic, there was a single study estimate of SMD -0.27 (N = 60, 1 RCT, 95% CI -0.78 to 0.23), indicating a tendency of better outcomes in verum than placebo treated patients.

For mood stabilisers and antidepressants, there were two single estimates of small studies available. Both tended to suggest a worse outcome following drug treatment, but neither was significant (valproate semisodium: SMD 0.52, N = 16, 1 RCT, 95% CI -0.63 to 1.67; fluoxetine: SMD 0.44, N = 20, 1 RCT, 95% CI -0.46 to 1.33).

The impact of omega-3 fatty acids on suicidal ideation was assessed by one RCT. There, significantly less patients who had received omega-3 fatty acids reported at least slight or more severe suicidal tendencies (RR 0.52, N = 49, 1 RCT, 95% CI 0.28 to 0.95).

In summary, the findings indicate that drug treatment may not only have no substantial effect of decreasing suicidal ideation but may even result in worsening of suicidal ideation, or at least in less favourable outcomes, as compared to placebo treatment. However, this estimation is only based on single study findings for valproate semisodium and fluoxetine. For olanzapine, several estimates are available, with one small significant effect in favour of olanzapine and a medium significant effect against it, and yet another study supporting this tendency. There was a significant beneficial effect for omega-3 fatty acids as reported by one study.

1.7 Suicidal behaviour

There was a significant single study estimate for the reduction of suicidal behaviour by the first-generation antipsychotic flupenthixol decanoate (RR of suicidal behaviour 0.49, N = 37, 1 RCT, 95% CI 0.26 to 0.92).

Another RCT of olanzapine assessed the frequency of suicidal episodes. Again, olanzapine treated patients had unfavourable results as compared to placebo, resulting in a non-significant SMD of 0.15 (N = 60, 1 RCT, 95% CI -0.36 to 0.65). No significant effect was found for the antidepressant mianserin sulfate (RR of suicidal behaviour 1.00, N = 58, 1 RCT, 95% CI 0.71 to 1.41).

In summary, there was a significant reduction in suicidal behaviour during flupenthixol decanoate treatment, a first-generation antipsychotic given as a long acting depot. Additionally, there was another study effect supporting by its direction the possible unfavourable effects of olanzapine for self-damaging tendencies in general, as previously seen for suicidality (cf. to 1.6 Suicidal ideation, above). The prevalence of suicidal behaviour was reported to be lower in mianserin treated patients, but not significantly.

1.8 Self-mutilating behaviour

There were two single study estimates for the second-generation antipsychotics aripiprazole and olanzapine, respectively. Both were non-significant but had opposite directions. Data indicated that patients treated with aripiprazole were less likely to engage in self-mutilating behaviour (RR 0.29, N = 52, 1 RCT, 95% CI 0.07 to 1.25), whereas olanzapine treated patients were not (RR 1.20, N = 24, 1 RCT, 95% CI 0.50 to 2.88). A comparable effect size was found for omega-3 fatty acids by one study (RR 1.23, N = 49, 1 RCT, 95% CI 0.51 to 2.97).

For the SSRI antidepressant fluoxetine, a SMD of 0.03 was found (N = 20, 1 RCT, 95% CI -0.85 to 0.92), indicating almost no difference between experimental and control group.

In summary, none of the available single study estimates yielded a significant effect. However, the possibility of more self-damaging behaviour in general under olanzapine treatment was, again, fortified (cf. to 1.6 Suicidal ideation and 1.7 Suicidal behaviour). Self-mutilating behaviour also occurred more often under omega-3 fatty acid supplementation as compared to placebo.

1.9 Affective instability

There was a significant decrease in affective instability by olanzapine treatment (mean change SD -0.16, N = 631, 3 RCTs, 95% CI -0.32 to -0.01, I^2 = 0%), but the effect was small in size. Another small but non-significant effect was found by one RCT for the second-generation antipsychotic ziprasidone (SMD -0.10, N = 60, 1 RCT, 95% CI -0.61 to 0.41).

One trial indicated a medium to large effect of the mood stabiliser lamotrigine (mean change SD -0.61, N = 27, 95% CI -1.39 to 0.17) and another trial showed a moderate to large effect of fluvoxamine, (SMD -0.64, N = 38, 1 RCT, 95% CI -1.30 to 0.01).

In summary, data indicated a significant (but small) effect of olanzapine in ameliorating affective instability, but no substantial effect for ziprasidone. Available data suggest that both lamotrigine and fluvoxamine may also be effective, but there are only single study effect estimates in each case with possibly too low power to detect statistical significance.

1.10 Chronic feelings of emptiness

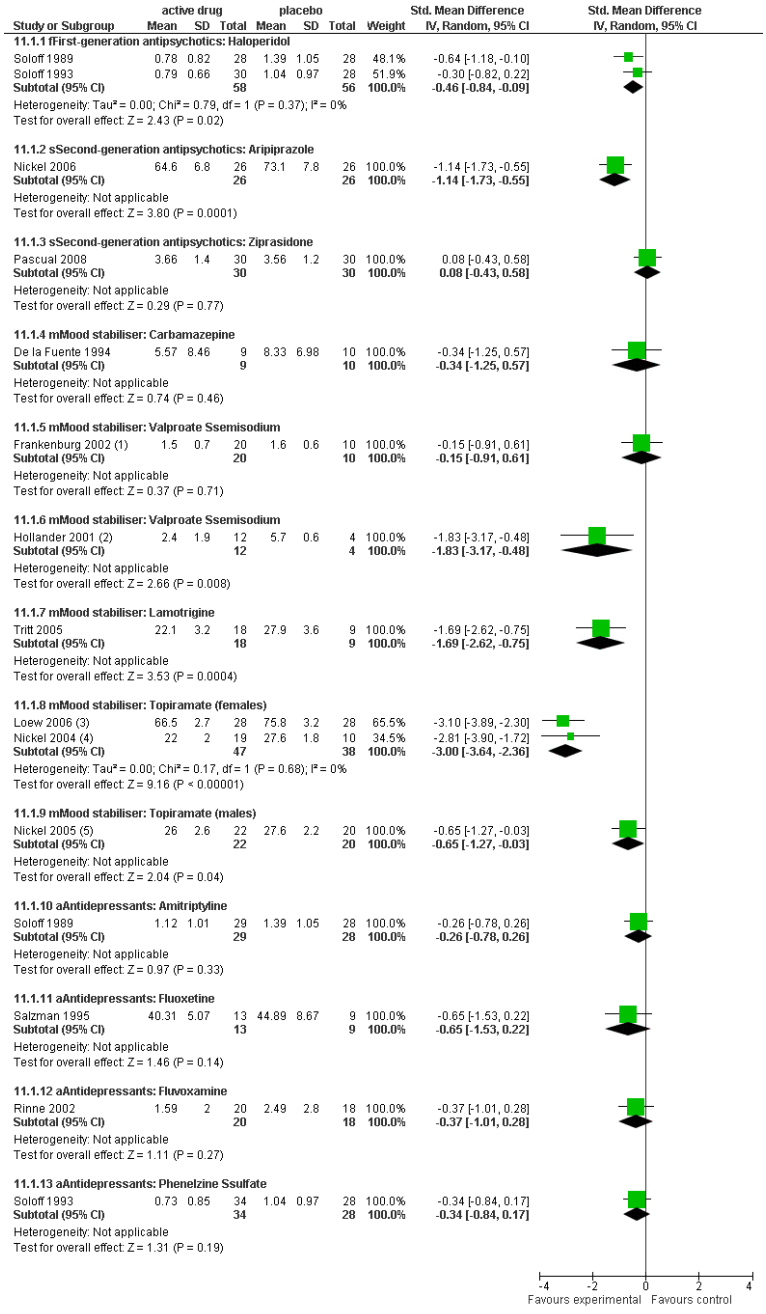
This outcome was only assessed in RCTs of second-generation antipsychotics, i.e. olanzapine and ziprasidone. For olanzapine, there was a minimal non-significant difference between olanzapine and placebo in terms of mean change SDs (-0.03, N = 631, 3 RCTs, 95% CI -0.22 to 0.16, I^2 = 23%). Ziprasidone treated patients felt slightly worse compared to patients who had been given placebo (SMD 0.18, N = 60, 1 RCT, 95% CI -0.32 to 0.69).

In summary, the evidence available for this outcome suggests no substantial effect of second-generation antipsychotics for this outcome.

1.11 Anger

SMDs are provided in Figure 5. For additional effect sizes, see Analysis 11.2 and Analysis 11.3.

Figure 5. Forest plot of comparison: 11.1 Active drug versus placebo: Anger, SMDs



(1) Frankenburg 2002 and Hollander 2001 were not pooled, as heterogeneity seemed considerable (I^2 78%), and could not definitely be expla
(2) cf. to (1)

(3) For Topiramate, data were analysed for male and female samples separately (I^2 of all three estimates 93%).
(4) cf. to (3)
(5) cf. to (3)

There was a significant effect for haloperidol treatment (SMD -0.46, N = 114, 2 RCTs, 95% CI -0.84 to -0.09, I^2 = 0%). Another first-generation antipsychotic, thiothixene, yielded no significant effect, as investigated by one RCT (SMD on basis of post-means and pre-SDs -0.07, N = 50, 1 RCT, 95% CI -0.63 to 0.48).

Usable data were also available for the second-generation antipsychotics aripiprazole, olanzapine, and ziprasidone. There was a large, significant effect for aripiprazole (SMD -1.14, N = 52, 1 RCT, 95% CI -1.73 to -0.55), and another significant effect for olanzapine (mean change SD -0.27, N = 631, 3 RCTs, 95% CI -0.43 to -0.12, I^2 = 0%). For ziprasidone, data suggested no beneficial effect (SMD 0.08, N = 60, 1 RCT, 95% CI -0.43 to 0.58).

For mood stabilisers, data indicated significant beneficial effects for any agent investigated here, with the exception of carbamazepine, where there was a positive but non-significant effect. Two RCTs tested valproate semisodium, but we did not pool the study estimates due to considerable heterogeneity (I^2 = 78%). Both RCTs indicated better results for their experimental groups as compared to placebo, but the difference was only significant in one case (Hollander 2001: SMD -1.83, N = 16, 1 RCT, 95% CI -3.17 to -0.48). There was another large effect for lamotrigine treatment (SMD -1.69, N = 27, 1 RCT, 95% CI -2.62 to -0.75). For topiramate, there were three RCTs available, two including women only, and one men. Each of the three study estimates favoured topiramate treatment significantly, but the size of effects varied. Therefore, all three estimates were considerably heterogeneous (I^2 = 93%), and we decided not to pool them. Instead, the two female samples were pooled, yielding a large overall effect estimate of SMD -3.00 (N = 85, 2 RCTs, 95% CI -3.64 to -2.36, I^2 = 0%). The effect of topiramate in the remaining male sample was smaller, but also significant (SMD -0.65, 1 RCT, 95% CI -1.27 to -0.03).

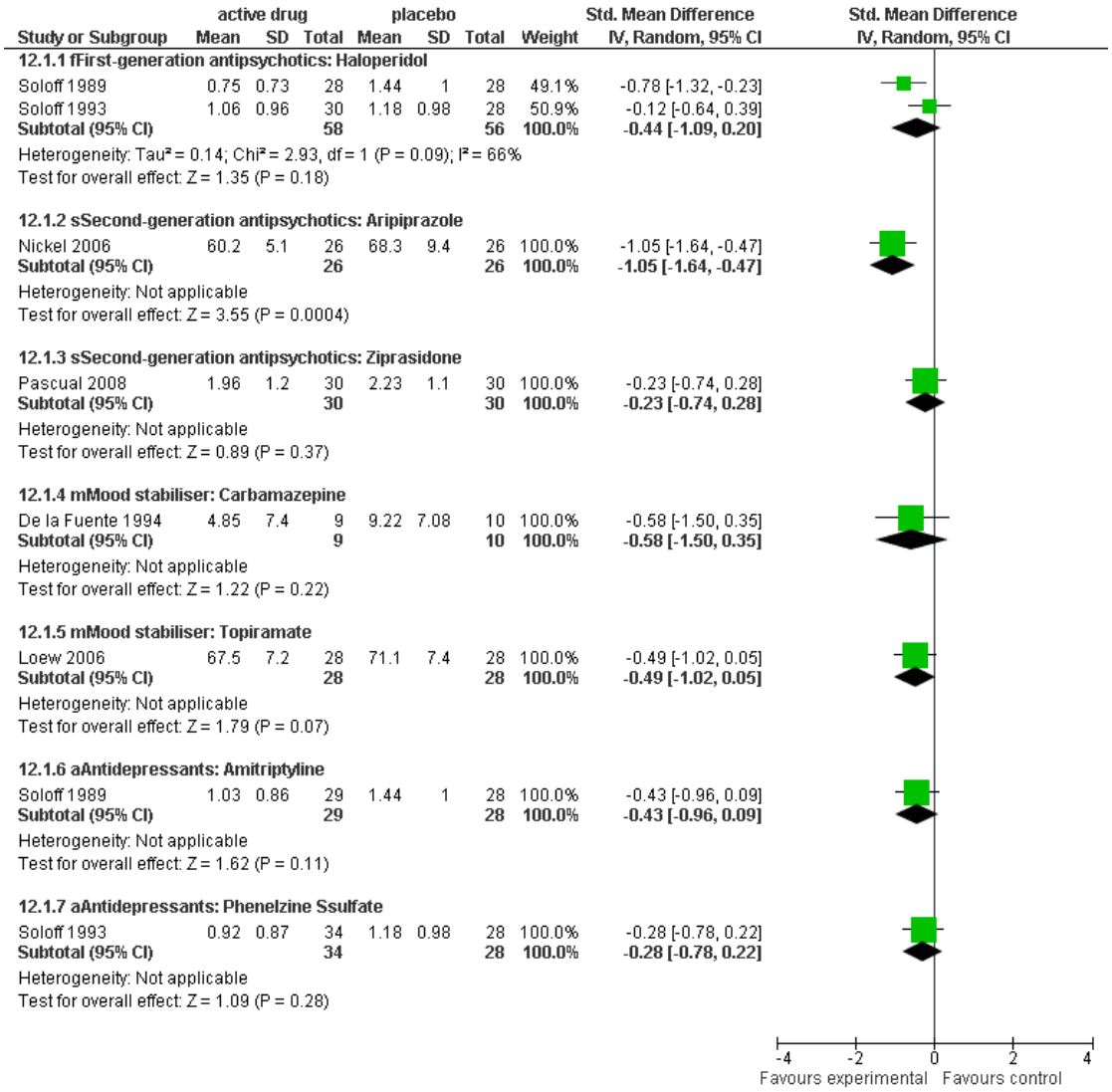
There were no significant effects for antidepressant treatment, i.e. the TCA amitriptyline, the SSRIs fluoxetine and fluvoxamine, and the MAOI phenelzine sulfate. Each estimate was based on one single study, though. Effect sizes were small to moderate in size (SMD -0.26 for amitriptyline to -0.65 for fluoxetine, see Figure 5).

In summary, data were available for first- and second-generation antipsychotics, mood stabilisers, and antidepressants. Significant effects were found for mood stabilisers (topiramate, valproate semisodium, lamotrigine) and second-generation antipsychotics (aripiprazole, olanzapine).

1.12 Psychotic symptoms

Findings indicated no significant beneficial effects for first-generation antipsychotics, mood stabilisers or antidepressants. With exception of haloperidol, all estimates were derived from single studies. However, all suggest better results for the experimental groups (see Figure 6 and Analysis 12.3), except of one trial of thiothixene (see Analysis 12.2).

Figure 6. Forest plot of comparison: 12.1 Active drug versus placebo: Psychotic symptoms, SMDs



There were significant effects for the second-generation antipsychotics aripiprazole (SMD -1.05, N = 52, 1 RCT, 95% CI -1.64 to -0.47) and olanzapine (mean change SD -0.18, N = 631, 3 RCTs, 95% CI -0.34 to -0.03, I^2 = 0%), but not for ziprasidone (see Figure 6 and Analysis 12.3).

In summary, data indicated significant benefits for second-generation antipsychotics only, i.e. for aripiprazole and olanzapine.

1.13 Dissociation

This outcome was only assessed by one RCT investigating the SSRI antidepressant fluoxetine. The study estimate indicated unfavourable results for fluoxetine treated patients, but the effect was not significant (SMD 0.42, N = 20, 1 RCT, 95% CI -0.47 to 1.32).

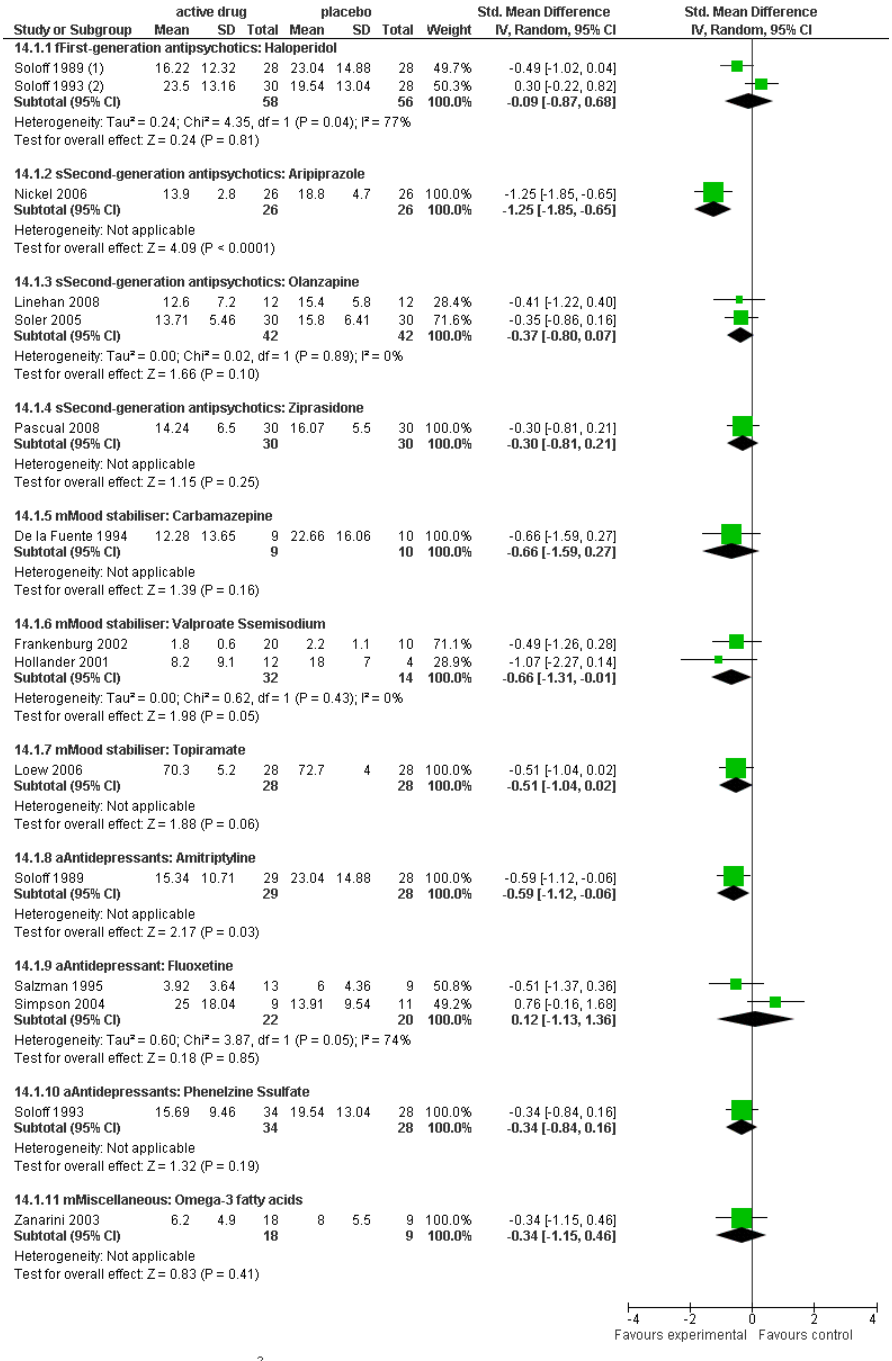
In summary, data for treatment of dissociative symptoms are scarce. Available data suggest that the antidepressant fluoxetine may not be beneficial in this regard.

Secondary outcomes

1.14 Depression

SMDs are provided in Figure 7. For additional effect sizes concerning thiothixene and olanzapine, see Analysis 14.2 to Analysis 14.4.

Figure 7. Forest plot of comparison 14.1 Active drug versus placebo: Depression, SMDs



(1) Despite of the high heterogeneity (I^2 77%), we decided to pool estimates, as clinical heterogeneity was quite low, and the same pattern of
(2) cf. to (1)

No significant effects were found for the first-generation antipsychotics haloperidol and thiothixene.

There was a large significant effect for the second-generation antipsychotic aripiprazole (SMD -1.25, N = 52, 1 RCT, 95% CI -1.85 to -0.65). No significant effects were found for olanzapine or ziprasidone.

Another significant effect was found for the mood stabiliser valproate semisodium (SMD -0.66, N = 46, 2 RCTs, 95% CI -1.31 to -0.01, I^2 = 0%). Single study estimates indicated better results for carbamazepine and topiramate as compared to placebo, but none yielded a significant effect.

Among antidepressant agents, a significant effect was only found for the TCA amitriptyline (SMD -0.59, N = 57, 1 RCT, 95% CI -1.12 to -0.06). For phenelzine sulfate, a MAOI, the direction of effect pointed to better outcomes for the experimental group as well, but not to a significant effect. The pooled estimate for the SSRI fluoxetine, however, indicated worse results for fluoxetine treated patients as compared to placebo (SMD 0.12, N = 42, 2 RCTs, 95% CI -1.13 to 1.36, I^2 = 74%).

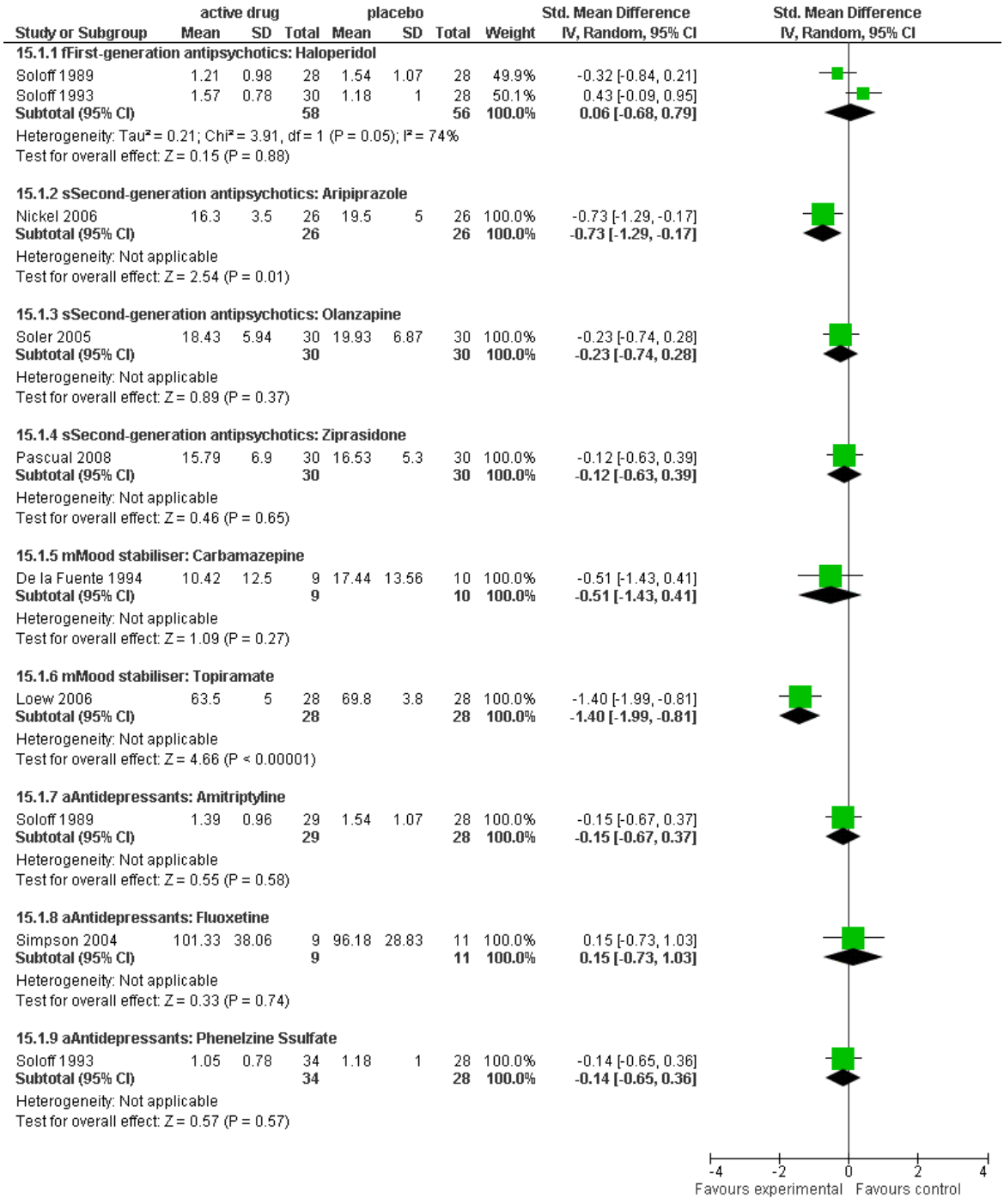
Omega-3 fatty acids were found to have beneficial effects by two trials. A non-significant yet favourable difference between the active treatment and placebo of SMD -0.34 (N = 30, 1 RCT, 95% CI -1.11 to 0.42) was found by one RCT. This finding was supported by another RCT reporting a significantly lower risk of non-responding in terms of a 50% reduction of depressive pathology if having received omega-3 fatty acids (RR 0.48, N = 49, 1 RCT, 95% CI 0.28 to 0.81).

In summary, agents of different classes of drugs were found to be effective in the treatment of depression (second-generation antipsychotic aripiprazole, mood stabiliser valproate semisodium, TCA amitriptyline, omega-3 fatty acids).

1.15 Anxiety

SMDs are given in Figure 8, for additional effect size calculations see Analysis 15.2.

Figure 8. Forest plot of comparison: 15.1 Active drug versus placebo: Anxiety, SMDs



No significant beneficial effects were found for the first-generation antipsychotic haloperidol or the antidepressant agents amitriptyline, fluoxetine, or phenelzine sulfate. Of the second-generation antipsychotics, aripiprazole was found to be significantly beneficial (SMD -0.73, N = 52, 1 RCT, 95% CI -1.29 to -0.17) as was olanzapine (mean change difference -0.22, N = 274, 1 RCT, 95% CI -0.41 to -0.03).

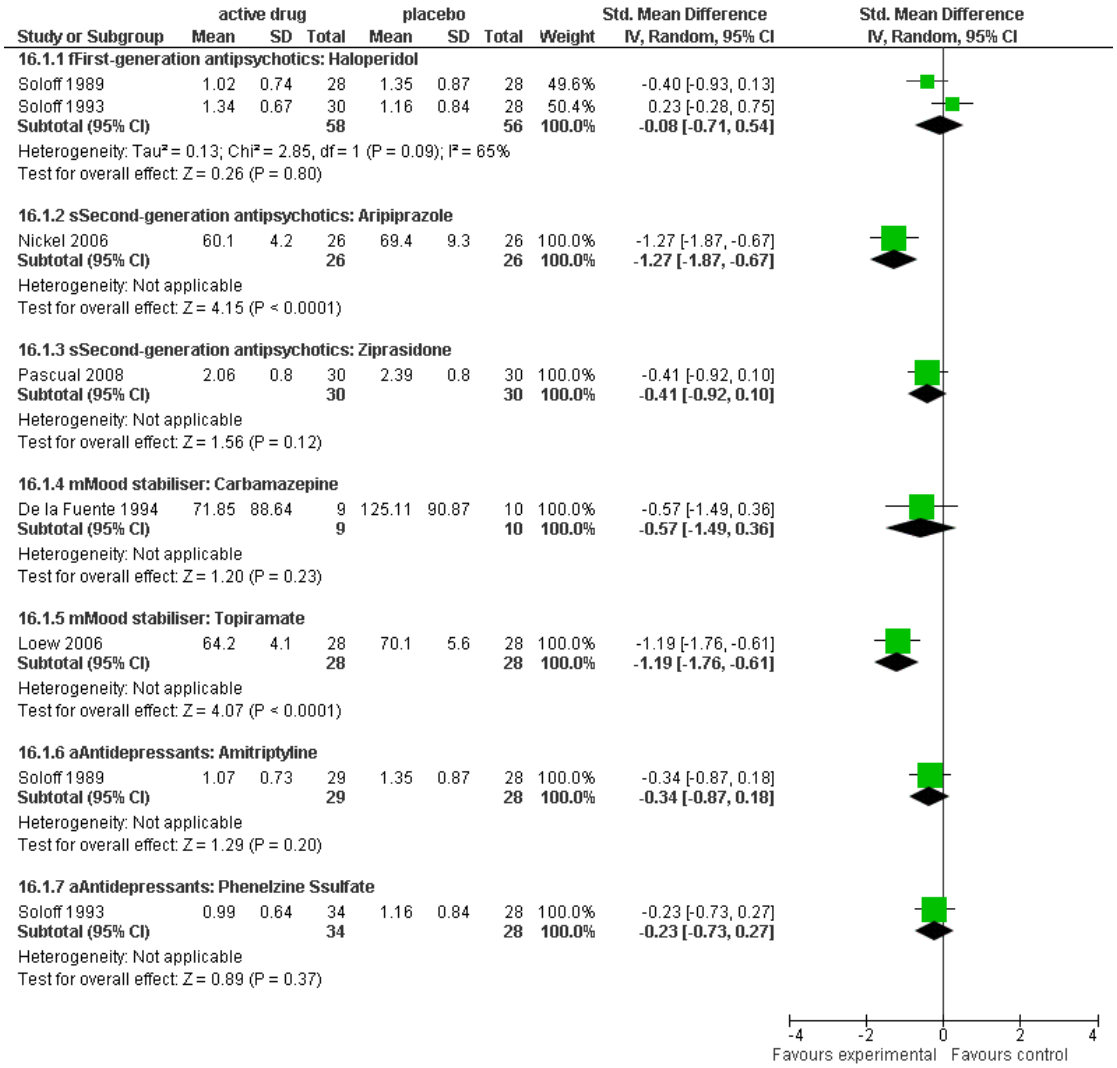
Additionally, a large significant effect was found for topiramate (SMD -1.40, N = 56, 1 RCT, 95% CI -1.99 to -0.81). Data indicated favourable results for carbamazepine treatment as well, with an effect of medium size, but this was not significant (SMD -0.51, N = 19, 1 RCT, 95% CI -1.43 to 0.41).

In summary, significant effects were found for second-generation antipsychotics (aripiprazole and olanzapine), and the mood stabiliser topiramate. These estimates are single study findings only.

1.16 General psychiatric pathology

SMDs are given in Figure 9, for additional effect size calculations see Analysis 16.2.

Figure 9. Forest plot of comparison: 16.1 Active drug versus placebo: General psychiatric pathology, SMDs



No significant beneficial effects were found for the first-generation antipsychotic haloperidol or the antidepressant agents amitriptyline and phenelzine sulfate. Of second-generation antipsychotics, aripiprazole was found to be significantly beneficial with a large effect of SMD -1.27 (N = 52, 1 RCT, 95% CI -1.87 to -0.67), but not so for olanzapine and ziprasidone. For these, the direction of effect did favour drug treatment though.

Additionally, another large significant effect was found for topiramate (SMD -1.19, N = 56, 1 RCT, 95% CI - 1.76 to -0.61). Data indicated favourable results for carbamazepine treatment as well, with an effect of medium size, but this was not significant (SMD -0.57, N = 19, 1 RCT, 95% CI -1.49 to 0.36).

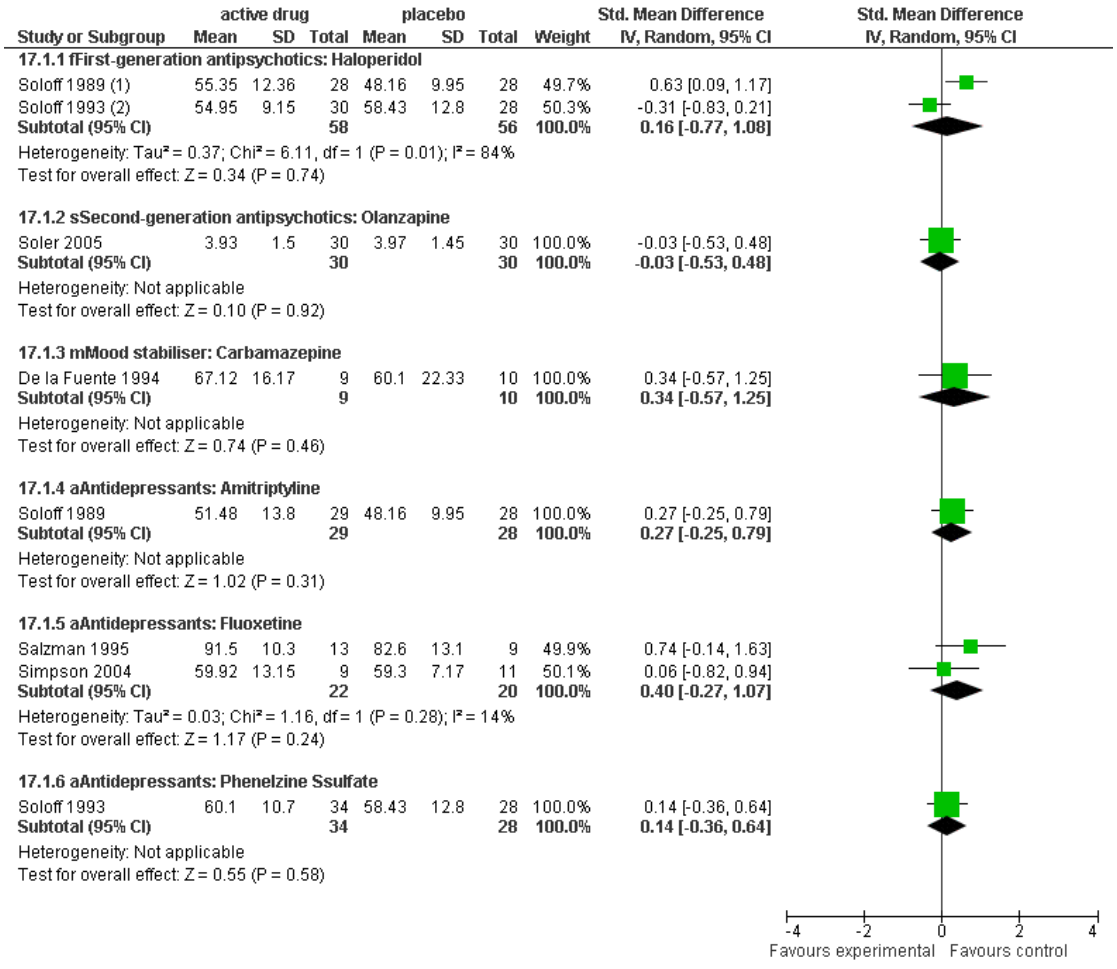
Small and non-significant effects were found for the antidepressant agents amitriptyline and phenelzine sulfate.

In summary, significant effects were found for the second-generation antipsychotic aripiprazole and the mood stabiliser topiramate. These estimates were derived from single studies each.

1.17 Mental health status

SMDs are given in Figure 10, for additional effect size calculations see Analysis 17.2 to Analysis 17.4. For this outcome, positive values of effect sizes indicate an amelioration, i.e. an increase of functioning by drug treatment.

Figure 10. Forest plot of comparison: 8.1 Active drug versus placebo: Mental health status, SMDs



(1) Despite of the high heterogeneity (I^2 84%), we decided to pool estimates, as clinical heterogeneity was quite low, and the same pattern of
(2) cf. to (1)

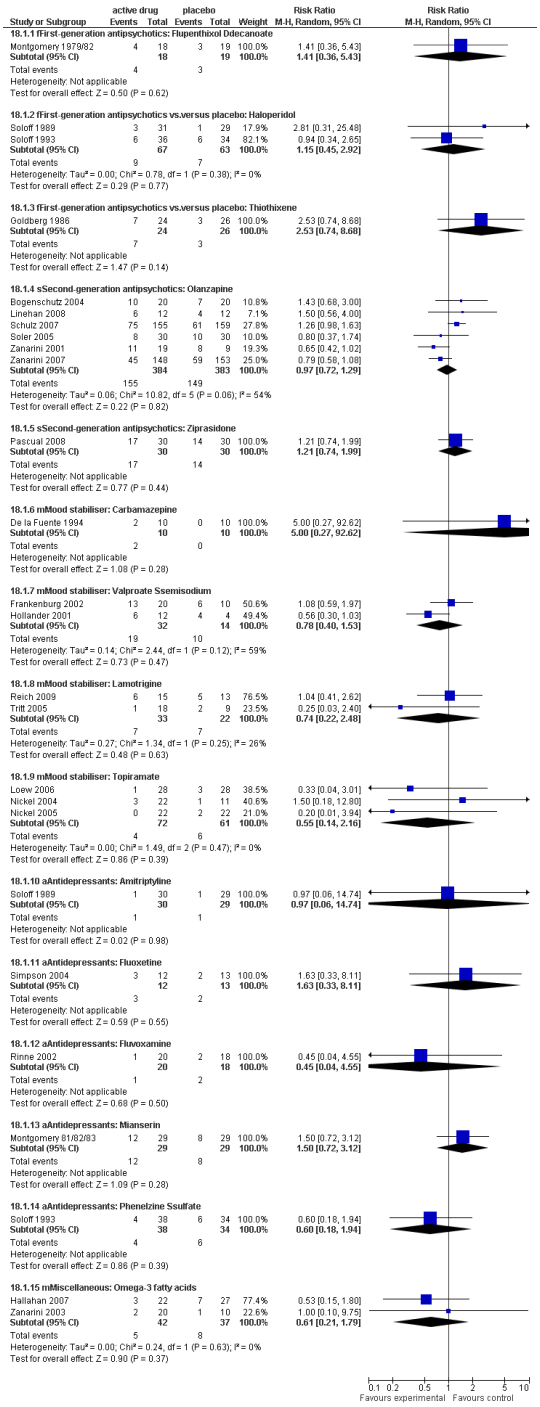
Data were available for first-generation antipsychotics haloperidol and thiothixene, the second-generation antipsychotic olanzapine, the mood stabilisers carbamazepine and valproate semisodium, and the antidepressant agents amitriptyline, fluoxetine, and phenelzine sulfate. The effect sizes were small to medium in size but none was significant.

In summary, available data do not suggest a significant increase of overall functioning by any of the investigated drugs.

1.18 Attrition

Overal tolerability was assessed in terms of the risk of not completing the study per protocol. Risk ratios of leaving the study early are given in Figure 11.

Figure 11. Forest plot of comparison: 18.1 Active treatment versus placebo: Attrition, RRs



Attrition did not differ significantly between experimental and control groups for any other drug versus placebo comparison. Lower drop-out rates for active drug treatment as compared to placebo were found for olanzapine, valproate semisodium, lamotrigine, topiramate, amitriptyline, fluvoxamine, phenelzine sulfate, and omega-3 fatty acids. No usable data of attrition were available for the comparison of aripiprazole versus placebo.

In summary, available data indicated that none of the active drugs was less well tolerated than placebo.

1.19 Adverse effects

Adverse effects outcomes will be reported separately by drug classes.

1.19.1 First-generation antipsychotics

There was a non-significant effect of haloperidol reducing body weight (SMD -0.18, N = 58, 1 RCT, 95% CI -0.70 to 0.34). For thiothixene or flupenthixol decanoate treatment, no adverse effects data were reported.

1.19.2 Second-generation antipsychotics

No usable data were available for aripiprazole treatment.

Detailed data were available for olanzapine. There was a significant effect of weight gain (SMD 1.05, N = 752, 6 RCTs, 95% CI 0.90 to 1.20, I^2 = 0%). The ratio of study participants reporting any adverse event was not significantly increased among olanzapine treated patients as compared to placebo (RR 1.13, N = 615, 2 RCTs, 95% CI 1.00 to 1.28, I^2 = 0%), but single events were: increased appetite was significantly more often reported in olanzapine groups (RR 2.78, N = 615, 2 RCTs, 95% CI 1.75 to 4.34, I^2 = 0%) as was somnolence (RR 2.97, N = 215, 2 RCTs, 95% CI 1.75 to 5.03, I^2 = 0%) and mouth-dryness (RR 2.24, N = 615, 2 RCTs, 95% CI 1.08 to 4.67, I^2 = 0%). Sedation had been assessed by two trials (Schulz 2007; Zanarini 2001), but we decided not to pool the two estimates because of considerable statistical heterogeneity (I^2 = 82%), that may have been due to the different observation periods (12 weeks versus 24 weeks) and sample sizes (N = 314 versus N = 28). Schulz 2007 reported sedation as significantly more often experienced by olanzapine treated patients (RR 9.23, N = 314, 1 RCT, 95% CI 2.18 to 39.12), while Zanarini 2001's findings supported the direction of effect (RR 1.26, N = 27, 1 RCT, 95% CI 0.44 to 3.66). The following adverse events were also reported but not found to occur significantly more often under olanzapine treatment: headache (RR 0.91, N = 615, 2 RCTs, 95% CI 0.43 to 1.92, I^2 = 67%), disturbed attention (RR 11.37, N = 301, 1 RCT, 95% CI 0.63 to 203.81), fatigue (RR 2.04, N = 615, 2 RCTs, 95% CI 0.79 to 5.23, I^2 = 54%), insomnia (RR 0.68, N = 615, 2 RCTs, 95% CI 0.33 to 1.37, I^2 = 15%), anxiety (RR 0.90, N = 314, 1 RCT, 95% CI 0.33 to 2.42), nausea (RR 0.83, N = 615, 2 RCTs, 95% CI 0.43 to 1.59, I^2 = 1%), constipation (RR 6.50, N = 28, 1 RCT, 95% CI 0.41 to 104.20), and nasopharyngitis (RR 0.62, N = 301, 1 RCT, 95% CI 0.23 to 1.66).

Detailed data were also available for laboratory value and vital sign changes. Therefore, all following effect estimates are based on baseline to endpoint change data. Significant changes were found for liver function tests, blood lipids, the haemogram, and calcium. For liver function parameters, the following effect estimates were found (all significant): AST/SGOT change: SMD 0.35, N = 526, 2 RCTs, 95% CI 0.18 to 0.52, I^2 = 0%; ALT/SGPT change: SMD 0.46, N = 530, 2 RCTs, 95% CI 0.29 to 0.63, I^2 = 0%; GGT (GGPT/SGGT/YGGT) change: SMD 0.26, N = 268, 1 RCT, 95% CI 0.02 to 0.50; total bilirubin change: SMD -0.29, N = 264, 1 RCT, 95% CI -0.53 to -0.05; direct bilirubin change: SMD -0.35, N = 158, 1 RCT, 95% CI -0.60 to -0.11). The following blood lipid changes were reported (all significant): total cholesterol change: SMD 0.42, N = 327, 2 RCTs, 95% CI 0.20 to 0.64, I^2 = 0%; LDL cholesterol change: SMD 0.35, N = 259, 1 RCT, 95% CI 0.10 to 0.59; HDL cholesterol change: SMD -0.28, N = 269, 1 RCT, 95% CI -0.52 to -0.04; triglycerides (fasting) change: SMD 0.37, N = 203, 1 RCT, 95% CI 0.09 to 0.64. There was also a significant effect for prolactin change (SMD 0.41, N = 528, 2 RCTs, 95% CI 0.23 to 0.59, I^2 = 10%). There were some significant differences in changes of haemogram parameters: leukocyte count change: SMD -0.40, N = 262, 1 RCT, 95% CI -0.65 to -0.16; neutrophils (segmented) change: SMD -0.39, N = 262, 1 RCT, 95% CI -0.63 to -0.14; basophils change: SMD -0.28, N = 262, 1 RCT, 95% CI -0.53 to -0.04; monocytes change: SMD -0.28, N = 262, 1 RCT, 95% CI -0.53 to -0.04. No significant differences in baseline to endpoint change were found for the following: erythrocyte count change: SMD -0.18, N = 262, 95% CI -0.42 to 0.06; haemoglobin change: SMD -0.21, N = 262, 1 RCT, 95% CI -0.45 to 0.03 and mean cell haemoglobin concentration change: SMD 0.03, N = 260, 1 RCT, 95% CI -0.22 to 0.27). For the platelet count change, conflicting results were reported, and effect estimates were not pooled because of considerable heterogeneity (I^2 = 90%). Despite having the same treatment durations, participants characteristics, and treatment doses, Schulz 2007 found a significant increase in the platelet count (SMD 0.32, N = 257, 1 RCT, 95% CI 0.07 to 0.56), whereas Zanarini 2007 reported a significant decrease (SMD -0.26, N = 260, 1 RCT, 95% CI -0.50 to -0.01). There was a significant effect for calcium change (SMD -0.33, N = 268, 1 RCT, 95% CI -0.57 to -0.09), but not for albumin change (SMD -0.21, N = 269, 1 RCT, 95% CI -0.45 to 0.03). There were no significant effects of olanzapine concerning kidney function parameters (creatine

phosphokinase change: SMD -0.21, N = 268, 1 RCT, 95% CI -0.45 to 0.03; urea nitrogen change: SMD -0.14, N = 269, 1 RCT, 95% CI -0.38 to 0.10) or vital signs changes (pulse, standing: SMD 0.08, N = 290, 1 RCT, 95% CI -0.15 to 0.31; pulse, supine: SMD 0.02, N = 290, 1 RCT, 95% CI -0.21 to 0.25; diastolic blood pressure, standing: SMD -0.03, N = 290, 1 RCT, 95% CI -0.26 to 0.20; diastolic blood pressure, supine: SMD -0.01, N = 290, 1 RCT, 95% CI -0.24 to 0.22; systolic blood pressure, standing: SMD 0.03, N = 290, 1 RCT, 95% CI -0.20 to 0.26; systolic blood pressure, supine: SMD -0.04, N = 290, 1 RCT, 95% CI -0.27 to 0.19).

For ziprasidone, data on single adverse events as reported by patients were available. There was no increased risk of experiencing any adverse event under ziprasidone treatment (RR 2.75, N = 60, 1 RCT, 95% CI 0.99 to 7.98). In detail, the following symptoms were reported more frequently by participants who had received ziprasidone, with no significant differences of frequency: dizziness (RR 9.00, N = 60, 1 RCT, 95% CI 0.51 to 160.17), sedation (RR 6.00, N = 60, 1 RCT, 95% CI 0.77 to 46.87), "uneasy feeling" (RR 7.00, N = 60, 1 RCT, 95% CI 0.38 to 129.93).

1.19.3 Mood stabilisers

For carbamazepine, no detailed data were available concerning adverse effects. For valproate semisodium and lamotrigine, body weight changes were given. No significant changes of body weight were observed for valproate semisodium (SMD 0.68, N = 30, 1 RCT, 95% CI -0.10 to 1.47) or lamotrigine (SMD -0.13, N = 27, 1 RCT, 95% CI -0.93 to 0.67).

There was a significant effect of body weight change by topiramate treatment, indicating significant weight loss (SMD -0.55, N = 127, 3 RCTs, 95% CI -0.91 to -0.19, I^2 = 0%). The following single adverse events were reported, with no significantly increased risk: memory problems (RR 2.00, N = 56, 1 RCT, 95% CI 0.55 to 7.22), trouble in concentrating (RR 2.00, N = 56, 1 RCT, 95% CI 0.55 to 7.22), headache (RR 1.00, N = 56, 1 RCT, 95% CI 0.15 to 6.61), fatigue (RR 2.00, N = 56, 1 RCT, 95% CI 0.40 to 10.05), dizziness (RR 1.50, N = 56, 1 RCT, 95% CI 0.27 to 8.30), menstrual pain (RR 1.67, N = 56, 1 RCT, 95% CI 0.44 to 6.31), and paraesthesia (RR 3.00, N = 56, 1 RCT, 95% CI 0.33 to 27.12).

1.19.4 Antidepressants

No detailed data of adverse effects were available for amitriptyline, fluoxetine, fluvoxamine, and mianserin. For phenelzine sulfate, a non-significant effect of weight gain was reported (SMD 0.11, N = 62, 1 RCT, 95% CI -0.39 to 0.61).

1.19.5 Miscellaneous active agents

No detailed data were available for the remaining active agent that had been included in this review, i.e. omega-3 fatty acids.

2. Drug versus drug comparisons

For corresponding analyses to drug versus drug comparisons, see Analysis 66.1 to Analysis 82.1.

In the following, results will be reported by comparison category.

2.1 First-generation antipsychotic versus first-generation antipsychotic

One RCT compared two first-generational antipsychotics, i.e. loxapine versus chlorpromazine (Leone 1982).

The participants of this trial were administered either loxapine (N = 40; mean daily dose 14.5 mg) or chlorpromazine (N = 40; mean daily dose 110 mg) for six weeks. Both male and female outpatients were included. Their mean age was 30.8 years. Severity of illness was rather low, as participants had to fulfil only four of the diagnostic BPD characteristics of Gunderson et al. (Gunderson 1981). Two of them had to be rated as severe and two as at least moderate.

Only tolerability and adverse events data were usable for effect size calculation. The ratio of patients who did not complete at least three weeks of treatment or were removed due to side effects did not differ significantly between either of the groups (RR of loxapine treated patients as compared to chlorpromazine treated patients 1.14, N = 80, 95% CI 0.46 to 2.85). Neither did the frequency of any adverse events differ significantly between the two groups (RR 1.14, N = 80, 95% CI 0.46 to 2.85), nor did any of the most frequent adverse events in particular (sleepiness/drowsiness: RR 0.80, N = 80, 95% CI 0.23 to 2.76; restlessness: RR 1.50, N = 80, 95% CI 0.26 to 8.50; muscle spasms: RR 3.00, N = 80, 95% CI 0.33 to 27.63; fainting spells: RR 0.14, N = 80, 95% CI 0.01 to 2.68).

2.2 First-generation antipsychotic versus antidepressant

Two RCTs compared haloperidol, a first-generational antipsychotic agent, with antidepressant medication. In the Soloff 1989 trial, the comparison treatment was the TCA amitriptyline, in the Soloff 1993 trial it was the MAOI phenelzine sulfate..

Patients in the Soloff 1989 trial received 4 to 16 mg/day of haloperidol (mean daily dose 4.8 mg/day, average plasma level 8.66 ng/ml, SD 3.7 ng/mL) or 100 to 175 mg/day of amitriptyline (mean daily dose 149.1 mg/day, average plasma level of 240.4 ng/mL amitriptyline + nortriptyline, SD 99.4). Patients (N = 61, both male and female, mean age 25.1 years) started as inpatients and were allowed to leave the hospital after two weeks. Nevertheless, almost two thirds (62%) completed as inpatients. Study duration was five weeks. With average GAS scores of 42.2 at baseline, the severity of illness was serious.

Data were available for interpersonal problems, impulsivity, anger, and psychotic paranoid symptoms. There were no significant effects for any primary outcome. Results indicated that patients tended to profit more from haloperidol treatment concerning interpersonal problems (SMD -0.14, N = 57, 95% CI -0.66 to 0.38), anger (SMD -0.36, N = 57, 95% CI -0.89 to 0.16), and psychotic paranoid symptoms (SMD -0.35, N = 57, 95% CI -0.87 to 0.18); and more from amitriptyline concerning impulsivity (SMD 0.20, N = 57, 95% CI -0.32 to 0.72). Neither drug proved to be significantly superior to the other one for any other pathology related outcome. Favourable results were found for haloperidol concerning anxiety (SMD -0.18, N = 57, 95% CI -0.70 to 0.34) and general psychiatric pathology (SMD -0.07, N = 57, 95% CI -0.59 to 0.45) as well as for amelioration of mental health status (SMD 0.29, N = 57, 95% CI -0.23 to 0.81). Depressive pathology responded slightly better in amitriptyline treated patients (SMD 0.08, N = 57, 95% CI -0.44 to 0.59). The risk of dropping out was higher in the haloperidol treated group (RR 2.90, N = 61, 95% CI 0.32 to 26.38), but again this was not statistically significant.

Soloff 1993 tested up to 4 mg of haloperidol (average dose 3.93 mg/day, SD 0.65, mean plasma level 5.29 ng/mL, SD 5.05) against up to 90 mg/day of the MAOI phenelzine sulfate (average dose 60.45 mg/day, SD 9.55, 77.54% mean platelet MAO inhibition after three weeks) in male and female BPD patients (N = 64, mean age: 26.7 years, SD = 7.2) for a duration of five weeks. All patients started as inpatients and remained in hospital for at least two weeks. With average GAS scores of 43.9 at baseline, the severity of illness was serious.

There were no significant differences between the two drugs concerning primary outcomes. The results indicated a tendency for haloperidol treated patients to suffer less from interpersonal problems as compared to phenelzine sulfate treated patients (SMD -0.46, N = 64, 95% CI -0.96 to 0.04). In all other cases, i.e. concerning BPD severity (SMD 0.46, N = 64, 95% CI -0.03 to 0.96), impulsivity (SMD 0.09, N = 64, 95% CI -0.04 to 0.58), anger (SMD 0.08, N = 64, 95% CI -0.41 to 0.57), and psychotic/paranoid symptoms (SMD 0.15, N = 64, 95% CI -0.34 to 0.64), phenelzine sulfate treated patients were better off.

Significant effects were found in favour of phenelzine sulfate treatment for depression (SMD 0.68, N = 64, 95% CI 0.17 to 1.19), anxiety (SMD 0.66, N = 64, 95% CI 0.15 to 1.16), general psychiatric pathology (SMD 0.53, N = 64, 95% CI 0.03 to 1.03) and mental health status (SMD -0.51, N = 64, 95% CI -1.01 to -0.01), with medium effect sizes. The risk of dropping out was higher in the haloperidol group (RR 1.58, N = 74, 95% CI 0.49 to 5.15), but the effect was not significant. Haloperidol treated patients experienced less weight gain than amitriptyline treated patients did (SMD -0.29, N = 64, 95% CI -0.78 to 0.21), but the effect was not significant.

2.3 Second-generation antipsychotic versus antidepressant

One RCT (Zanarini 2004) compared the second-generation antipsychotic olanzapine to the SSRI antidepressant fluoxetine. All participants were female outpatients (N = 30, mean age: 23.0 years, SD = 5.7), receiving either 2.5 mg/day of olanzapine or 10.0 mg/day of fluoxetine for a duration of eight weeks. With average GAF scores of 52.5 (SD = 6.9), the patients were moderately ill.All SMD effect sizes were calculated on the basis of mean baseline change scores. Dichotomous data were calculated on basis of the ITT sample as intended.

There were no significant differences between the two drugs for any pathology-related outcome. Usable data were provided for impulsivity, with a small, non-significant effect favouring olanzapine (mean change SMD -0.20, N = 29, 95% CI -0.93 to 0.53). Olanzapine treated patients also experienced a greater decrease in depressive pathology (SMD -0.73, N = 29, 95% CI -1.49 to 0.03), but the effect was, again, not significant. Attrition did not differ significantly between the groups (RR 0.29, N = 30, 95% CI 0.20 to 1.76). The only significant findings referred to adverse effects of treatment, with higher weight gain (SMD 0.98, N = 29, 95% CI 0.20 to 1.76) and more cases of mild sedation (RR 3.50, N = 30, 95% CI 1.23 to 9.92) in olanzapine treated patients. Akathisia was also more often reported by olanzapine treated patients, but the effect estimate was not significant (RR 0.70, N = 30, 95% CI 0.23 to 2.11).

3. Drug versus combination of drugs

The Zanarini 2004 RCT comprised three experimental groups. One group received the second-generation antipsychotic olanzapine (2.5 mg/day; N = 16), another group received the SSRI antidepressant fluoxetine (10 mg/day; N = 14), and the third group received both drugs (2.5 mg/day of olanzapine plus 10.0 mg/day; N = 15) for eight weeks. All participants were female outpatients (mean age: 23.0 years, SD = 5.7). With average GAF scores of 52.5 (SD = 6.9), they were moderately ill.

All SMD effect sizes were calculated on basis of mean baseline change scores. Dichotomous data were calculated on basis of the ITT sample as intended.

Only small and non-significant differences were found between olanzapine treatment alone and combined treatment with fluoxetine (impulsivity: mean change SMD 0.02, N = 29, 95% CI -0.71 to 0.76, "favouring" combined treatment; depression: mean change SMD -0.26, N = 29, 95% CI -1.00 to 0.47, favouring olanzapine alone). Neither attrition (RR 0.19, N = 31, 95% CI 0.01 to 3.63), nor weight gain (SMD 0.70, N = 29, 95% CI -0.05 to 1.46) differed significantly between the two groups . There were no significant differences in the ratio of participants reporting sedation (RR 1.61, N = 31, 95% CI 0.87 to 2.96) or akathisia (RR 0.75, N = 31, 95% CI 0.25 to 2.28) between the groups.

For the comparison of fluoxetine versus combined treatment with olanzapine, again there were no significant differences. However, both effect estimates of pathology-related outcomes indicated bet-

ter results for combined treatment than fluoxetine alone (impulsivity: mean change SMD 0.25, N = 26, 95% CI -0.53 to 1.02; depression: mean change SMD 0.54, N = 26, 95% CI -0.24 to 1.33). For tolerability, body weight change and sedation, data indicated better results for the group that had received fluoxetine alone (attrition: RR 0.54, N = 29, 95% CI 0.05 to 5.28; body weight change: SMD -0.54, N = 29, 95% CI -1.32 to 0.25; sedation: RR 0.46, N = 29, 95% CI 0.15 to 1.44). Akathisia was more often experienced by the participants with single treatment (RR 1.07, N = 29, 95% CI 0.39 to 2.92).

DISCUSSION

Summary of main results

1. Drug versus placebo

The following placebo comparisons were investigated in the identified RCTs.
(1) First-generation antipsychotics:
(a) thiothixene (Goldberg 1986, N = 50);
(b) flupenthixol (Montgomery 1979/82, N = 30);
(c) haloperidol (Soloff 1989, N=60; Soloff 1993, N = 58).
(2) Second-generation antipsychotics:
(a) aripiprazole (Nickel 2006, N = 52);
(b) olanzapine (Bogenschutz 2004, N = 40; Linehan 2008, N = 24; Schulz 2007, N = 314; Soler 2005, N = 60; Zanarini 2001, N = 28; Zanarini 2007, N = 301);
(c) ziprasidone (Pascual 2008, N = 60).
(3) Mood stabilisers:
(a) carbamazepine (De la Fuente 1994, N = 20);
(b) valproate semisodium (Frankenburg 2002, N = 30; Hollander 2001, N = 16);
(c) lamotrigine (Reich 2009; Tritt 2005, N = 27);
(d) topiramate (Loew 2006, N = 56; Nickel 2004 and Nickel 2005, N = 31 + N = 44).
(4) Antidepressants:
(a) amitriptyline (Soloff 1989, N = 59);
(b) fluoxetine (Salzman 1995, N = 22, Simpson 2004, N = 25);
(c) fluvoxamine (Rinne 2002, N = 38);
(d) phenelzine sulfate (Soloff 1993, N = 72);
(e) mianserin (Montgomery 81/82/83, N = 38).
(5) Miscellaneous:
(a) omega-3 fatty acid (Hallahan 2007, N = 49; Zanarini 2003, N = 30).

1.1 Pathology related outcomes

Of the first-generation antipsychotics under investigation, haloperidol had a significant effect concerning the reduction of anger, and flupenthixol treated patients were significantly less likely to get engaged in suicidal acts. No proof of efficacy was found for thiothixene.
Of the second-generation antipsychotics, aripiprazole had significant effects in the reduction of interpersonal problems, impulsivity, anger, psychotic paranoid symptoms, depression, anxiety, and general psychiatric pathology. For olanzapine, no significant effects were found for any pathology related outcome in primary analyses. Secondary analyses indicated significant decreases in affective instability, anger, psychotic paranoid symptoms, and anxiety. A significantly greater decrease in anxiety by olanzapine was found by one trial. Concerning suicidal ideation and self-mutilating behaviour, only two of the five relevant study results could be pooled due to different formats of reporting. The pooled effect of these two estimates suggests that the olanzapine-treated group experienced a significantly lower degree of amelioration of recurrent suicidal ideation as compared to the placebo group. Of the remaining three trials reporting on self-harming behaviour, two also found non-significant tendencies of unfavourable outcomes for olanzapine. No significant effects were found for ziprasidone treatment.
There were also significant effects for the mood stabilisers valproate semisodium, lamotrigine, and topiramate. Valproate semisodium had significant effects concerning the reduction of interpersonal problems and depression. A significant effect in the reduction of anger was found by one study, and the positive direction of effect was supported by the findings of another study. Lamotrigine was significantly superior to placebo concerning impulsivity and anger. Topiramate had significant effects concerning interpersonal problems, impulsivity, anger (as assessed by three single, significant study effects, only two of which could be pooled), anxiety, and general psychiatric pathology. No significant effects were found for carbamazepine treatment.
For antidepressants, there was only a significant effect for the TCA amitriptyline concerning the reduction of depression. No significant effects were found for mianserin, the SSRI agents fluoxetine and fluvoxamine, nor for the MAOI agent phenelzine sulfate.
Omega-3 fatty acid was found to have a significant effect on suicidality. For depression, a significant effect was found by one study, with the second study (that could not be pooled with the first one due to different formats of data reporting) supporting the direction of effect.

1.2 Adverse effects

Tolerability did not differ for any drug placebo comparison, i.e. drug treatment was not associated with a higher rate of non-completers than was placebo treatment.
Most trials did not provide numerical data on specific adverse effects, with the exception of body weight changes. Haloperidol and phenelzine treatment had no significant effects on body weight, nor did valproate semisodium or lamotrigine. However, olanza-

pine treatment was associated with significant weight gain, and topiramate treatment with significant weight loss. The ratio of olanzapine, ziprasidone and lamotrigine treated patients reporting any adverse event did not differ significantly as compared to the placebo groups.

Numerous data on additional specific adverse effects were only available for a few trials. For the placebo comparisons of ziprasidone and topiramate, single adverse events were reported, with no significant differences in occurrence between the groups. Detailed data were available for olanzapine, including even changes in laboratory values. Here, the ratio of participants reporting any adverse event in each group did not differ significantly between olanzapine and placebo treatment. However, olanzapine treated patients reported significantly more often increased appetite, somnolence, and mouth-dryness. One trial reported significantly more sedation in olanzapine treated patients, and another one (that could not be pooled with the first one due to substantial heterogeneity) supported this direction of effect. Additionally, significant effects on liver values, blood lipids, prolactin levels, and full blood counts were found, but there were no significant effects on kidney function values or cardiovascular system parameters.

However, little is known about adverse events increasing the risk of patients not completing treatment or experiencing body weight changes, except for olanzapine treatment. Therefore, the above cited significant effects should be regarded with caution. Known adverse effects of the remaining drugs have certainly also to be considered when choosing a treatment option for a certain patient, though the data were too sparse to calculate effect sizes in this review for most drugs.

2. Drug versus drug

The following drug versus drug comparisons were investigated (numeration as in results section for ease of comparison).

(6) First-generation antipsychotic versus first-generation antipsychotic:

(a) loxapine versus chlorpromazine (Leone 1982, N = 40).

(7) First-generation antipsychotic versus antidepressant:

(a) haloperidol versus amitriptyline (Soloff 1989, N = 61);

(b) haloperidol versus phenelzine sulfate (Soloff 1993, N = 74).

(8) Second-generation antipsychotic versus antidepressant:

(a) olanzapine versus fluoxetine (Zanarini 2004, N = 30).

2.1 Pathology related outcomes

Concerning the comparison of the two first-generation antipsychotics loxapine versus chlorpromazine, there were no usable data available regarding any pathology related outcome.

The first-generation antipsychotic haloperidol and the antidepressant amitriptyline did not differ significantly concerning any primary or secondary outcome. The antidepressant phenelzine sulfate proved to be superior to haloperidol in reducing depression, anxiety, general psychiatric pathology, and improving the overall mental health status.

No significant differences were found for the comparison of the second-generation antipsychotic olanzapine with the antidepressant fluoxetine for any pathology related outcome.

2.2 Adverse effects

Tolerability, i.e. attrition, did not differ significantly for any of the investigated drug versus drug comparisons.

The comparison of the frequencies of adverse events (i.e. any adverse event, sleepiness, restlessness, muscle spasms, fainting spells) in loxapine and chlorpromazine treated patients yielded no significant differences.

No data of adverse effects were available for the comparison of haloperidol versus amitriptyline. For the haloperidol versus phenelzine sulfate comparison, weight change was reported, with no significant difference between the two treatments.

However, olanzapine and fluoxetine treatment differed significantly concerning weight gain, with more weight gain in the olanzapine treated group. Additionally, a higher ratio of olanzapine treated patients reported mild sedation, as compared to the fluoxetine group.

3. Active drug versus combination of drugs

The following comparisons were investigated (numeration following on from 2. Drug versus drug, above).

(9) Second-generation antipsychotic versus second-generation antipsychotic plus antidepressant:

(a) olanzapine versus olanzapine plus fluoxetine (Zanarini 2004, N = 31).

(10) Antidepressant versus antidepressant plus second-generation antipsychotic:

(a) fluoxetine versus fluoxetine plus olanzapine (Zanarini 2004, N = 29).

3.1 Pathology related outcomes

For both the comparisons olanzapine versus olanzapine plus fluoxetine as well as fluoxetine versus fluoxetine plus olanzapine, data on impulsivity and depressive pathology were available. There were no significant differences indicating any benefits from combined treatment versus treatment with olanzapine or fluoxetine alone.

3.2 Adverse effects

There were no significant differences for both comparisons in terms of tolerability, body weight change, and the frequency of restlessness or mild sedation.

Overall completeness and applicability of evidence

Participants

As described earlier (see Characteristics of included studies table), most study participants exhibited mild to moderate levels of illness. However, there was a broad range from seriously ill (e.g. Soloff 1989: mean GAS value pre-treatment 42.2, reflecting "serious symptomatology or impairment in functioning") to very mildly impaired patients (e.g. Zanarini 2001: "patients [...] leading active social and vocational lives"). Acutely suicidal patients were not included in most trials, with the exception of Montgomery 1979/82 and Montgomery 81/82/83, including patients immediately following a severe suicidal act that had led to hospital admission.

Of concern regarding applicability to clinical settings might be the psychiatric exclusion criteria of most studies. Besides acutely suicidal patients, people with comorbid schizophrenia or schizoaffective disorders, bipolar disorders, alcohol or drug dependence and sometimes even alcohol or drug abuse were often not eligible for study participation. What is more, a current major depressive episode or severe depression was also a criterion of exclusion in the majority of trials. As comorbid axis-I disorders are highly prevalent in BPD patients, especially mood disorders (96.9%) and substance use disorders (62.1%; Zanarini 2004b), the exclusion of those participants renders applicability difficult. However, eating disorders, which are highly prevalent in BPD patients as well (53%, Zanarini 2004b), were no reason for exclusion in any study (with the exception of De la Fuente 1994; Salzman 1995, who excluded patients with any comorbid axis-I disorder). Anxiety disorders, which are prevalent in 89.0% of BPD patients (Zanarini 2004b), were only excluded in two trials (i.e. current PTSD, panic disorder, or obsessive-compulsive disorder; Schulz 2007; Zanarini 2007).

One third of trials was restricted to female patients (nine out of 27), one trial was restricted to men (Nickel 2005), and within the remaining samples, women were always predominant. Thus, women constituted the majority of all participants involved within this review. This reflects the overall higher prevalence of BPD diagnosis in women as compared to men (although the "real" prevalence is supposed to be even; Torgersen 2005), but may make the applicability to male patients difficult.

Interventions

Study duration ranged from 32 days to 24 weeks, with a mean duration of approximately 12 weeks. These observation periods may be sufficient to judge treatment efficacy in the single patient. However, drug treatment often lasts longer in clinical settings. Therefore, especially adverse effects must be monitored cautiously. Since most BPD patients are taking psychotropic medication continuously, future RCTs on this topic should cover appropriate observation periods of longer duration (e.g. six months as a rough navigation) to allow for better applicability to clinical settings.

Catamnestic data are only available for Loew 2006; Nickel 2004; Nickel 2005 (all: topiramate versus placebo), Tritt 2005 (lamotrigine versus placebo in female patients), and Nickel 2006 (aripiprazole versus placebo in both male and female patients) studies. As blinding was broken after the initial 8- and 10-week treatment phases in each of these trials, we decided not to include the catamnestic data here, as the break of blinding is likely to introduce bias on efficacy findings, especially on self-rated or self-reported data. For aripiprazole and lamotrigine, all significant findings of the post-treatment comparisons were still present after an additional 18 months of open treatment. Significant changes throughout the whole observation period were reported for all topiramate trials. All findings at post-treatment were corroborated by the catamnestic data, with exception of two outcome variables: There was no significant change for general psychiatric pathology concerning the overall observation period, and a significant change for depressive pathology emerged at the end of the 18-month follow-up.

Another difference to clinical settings may be that patients often receive several psychotropic drugs at a time. Polypharmacy is the rule rather than the exception (Zanarini 2004a). With the exception of the comparison of combined olanzapine and fluoxetine treatment to olanzapine and fluoxetine treatment alone (Zanarini 2004; no beneficial effects for combined treatment), there are no data from RCTs available supporting or even investigating polypharmacological treatment. As combined drug treatment cannot be considered as having the additional effect to that of each single drug treatment, it should always be considered that the administration of several drugs is not empirically supported by any RCT, and, to our knowledge, not by any trial of lower evidence level either.

With the exception of the Linehan 2008; Simpson 2004 and Soler 2005 trials, all patients of whom were in DBT treatment, the study participants did not receive specific concomitant psychotherapy, either because it was not allowed by the study protocol, or patients were allowed to receive psychotherapy but did not. However, mental health service treatment options vary internationally, i.e. receiving psychotherapy may be more characteristic for some countries and out of character for others.

There are some more substances that are currently discussed for use in BPD patients (especially second-generation antipsychotics), that could not be included in this review as RCTs are currently not available. However, there are some ongoing trials (see Characteristics of ongoing studies), the results of which will hopefully be included in subsequent versions of this review. Additionally, there are findings from lower-evidence studies on further second-generation antipsychotics (clozapine, quetiapine, risperidone), mood stabilisers (divalproex-extended release, lithium, oxcarbazepine), antidepressants (MAOI tranylcypromine, NRI reboxetine, SNRI venlafaxine, the SSRIs sertraline and paroxetine,

the TCAs desipramine and imipramine), anxiolytics (alprazolam), and miscellaneous drugs (clonidine, opioid antagonists naloxone and naltrexone, riluzole, and trifluoperazine).

Outcomes

Unfortunately, there was little consensus between primary studies on which outcome variables are crucial to rate therapy efficacy upon, even for those testing the same drug comparisons. Additionally, the use of different assessment instruments for one outcome variable renders comparability more difficult than necessary, and increases heterogeneity.

Mostly, outcome assessment was restricted to target variables that were not assessed with BPD-specific assessment instruments. For example, psychotic pathology was a common outcome, and common unspecific assessment instruments were used (i.e. SCL-90-subscale "psychoticism"), but BPD-specific psychotic pathology, i.e. stress-related paranoid ideation and dissociation, was not assessed. Hence, some domains of BPD core pathology were almost completely neglected, e.g. affective instability, dissociation, or chronic feelings of emptiness. Fortunately, relevant assessment instruments have been developed lately, reflecting each of the BPD core criteria (e.g. the BPDSI scale by Arntz 2003, the CGI-BPD scale by Perez 2007, or the ZAN-BPD scale by Zanarini 2003a).

Additionally, there were very few numerical data provided concerning adverse events. Some studies reported no details at all beyond attrition and body weight changes, whereas others only stated that adverse events were few and comparably frequent in all groups. We therefore appreciate the detailed reporting of adverse effects allowing for the calculation of treatment effects, and warn against regarding the other drugs, where relevant data are lacking, as safe, especially with regard to long-term therapy. We strongly recommend considering known adverse effects of all drugs when choosing a certain treatment option, although we were not able to report them here because of incomplete assessment or reporting of the primary studies investigated here.

Specificity of treatment effects

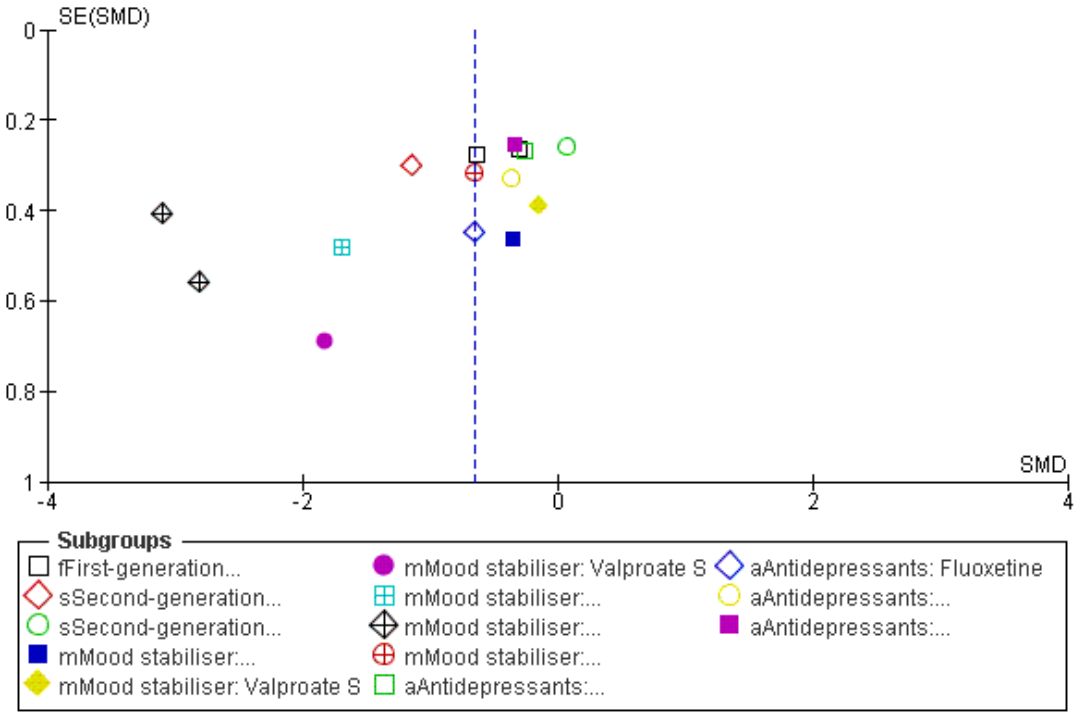
We cannot exclude that unspecific sedating effects, e.g. of valproate semisodium or olanzapine, may have contributed to study results. However, effects were also seen with non-sedating substances such as aripiprazole or lamotrigine questioning the broad conclusion that sedating effects are central for treatment effects.

Quality of the evidence

Altogether, 28 RCTs have been included, covering 22 different comparisons in ten comparison categories (see "Description of studies"). In the presence of the multitude of different comparisons and outcome variables, most results are based on single study findings only. The study sample sizes were rather small, and ranged, with exception of two large trials (Schulz 2007; N = 314; Zanarini 2007; N of patient data used here: 301), between 16 (Hollander 2001) and 108 (Soloff 1993; divided into three groups). Depending on the randomisation algorithm, i.e. if study groups were equal in size or one group twice as large as the other, and the overall number of treatment groups, the minimum group size was N = 4 (Hollander 2001) and the maximum group size was N = 43 (Nickel 2004; Nickel 2005). Therefore, the power to detect significant effects was quite low.

In addition, the overall robustness of findings must be considered low for the majority of comparisons. Because the current evidence embraces only one single RCT effect, further findings would be likely to affect the actual results, especially if including larger study samples. However, the influence of further trials cannot definitely be predicted: On the one hand, further primary studies would enhance power and therefore make the detection of significant effects more likely. On the other hand, the actual data are based on very few to single observations, so it is impossible to judge about publication biases (e.g. by depicting funnel plots as intended), even if the concealment of negative, non-significant findings is much more likely. In Figure 12, a funnel plot was drawn for the comparison category with most single study effects (comparison 11.1, SMDs of active drug versus placebo comparisons for the outcome "anger"). It is most difficult to draw definite conclusions from that figure, as it embraces a heterogeneous sample of effect sizes for diverse drug-placebo comparisons. On the one hand, there seems to be an overall tendency of lacking non-significant findings (no effect estimates at bottom right corner). On the other hand, the publication of additional RCTs matching the comparisons already investigated here is rather unlikely, as we are only aware of ongoing trials testing different drugs (see Characteristics of ongoing studies).

Figure 12. Funnel plot of comparison: 11.1 Active drug versus placebo: Anger, SMDs



Summary of findings tables including ratings of the evidence quality are provided for all drug versus placebo comparisons (see Appendix 14 to Appendix 29).

Potential biases in the review process

We strived to identify all relevant published and unpublished evidence (see Search methods for identification of studies). The search was not restricted to any language. In spite of the great efforts to avoid publication bias, we were not able to include any unpublished data.

As relating to our inclusion criteria, we tried to retain a most homogeneous pool of primary studies. However, there were some inconsistencies between studies particularly pertaining to psychiatric comorbidity of study participants. For example, bipolar disorders were a common exclusion criterion, whereas one study (Frankenburg 2002) required its participants to have a diagnosis of bipolar II disorder. Also, acute suicidal patients were not eligible for most studies, but the participants of the Montgomery 1979/82 and Montgomery 81/82/83 trials were recruited immediately following a suicidal act that had led to hospital admission. In nine studies, only women were included (Frankenburg 2002; Loew 2006; Nickel 2004; Rinne 2002; Simpson 2004; Tritt 2005; Zanarini 2001; Zanarini 2003; Zanarini 2004), whereas the remaining study samples consisted of both male and female patients.

The severity of illness also varied between studies, mostly from mild to moderate. However, we tried to exactly specify and describe all studies with regard to their crucial characteristics (see Description of studies, Characteristics of included studies), in order to let the reader decide about applicability of relevant study characteristics to his or her decisive situation.

Another point of concern is reporting bias. Most studies provide only a fragmentary outcome pattern, making the concealment of non-significant findings likely. We tried to deal with this by first defining all patient-relevant outcome variables that are directly (primary outcomes) or indirectly (secondary outcomes) associated with BPD treatment, i.e. all outcome variables that a consumer and his or her therapist are likely to be interested in. We have tried not only to stress reported findings but also outcome gaps, such as outcome variables for which the effects of a certain treatment cannot be judged due to a lack of data.

Agreements and disagreements with other studies or reviews

Other reviews

This is an update and new citation version of the preceding Cochrane Collaboration review 'Pharmacological interventions

for BPD' by Binks 2006. Its literature searches covered the period up to October 2002, and the latest included study dates from 2001. Since then, there have been further research activities, and new substances have been investigated in BPD. The preceding review included ten RCTs, whereas we were aware of 28 includable studies at the point of last literature search updates (September 2009).

As concerns other systematic reviews and meta-analysis on the topic of pharmacotherapy for BPD, we did not review this type of evidence systematically. However, there are three recent works, each with a similar focus, that should be referred to at this point (Duggan 2008; Ingenhoven 2010; Nosè 2006).Nosè 2006 Duggan 2008; Ingenhoven 2010

Both Nosè 2006Nosè 2006 and Ingenhoven 2010Ingenhoven 2010 included placebo-controlled RCTs. Mixed study samples with primarily BPD patients were includable in the Nosè 2006Nosè 2006 review, participants with both BPD and/or schizotypal PD were includable in the Ingenhoven 2010Ingenhoven 2010 review, and people with any PD were included in the Duggan 2008Duggan 2008 review. The most recent literature searches were done in June 2006, December 2007 and December 2006, respectively. Due to different inclusion criteria and different search periods, the study pools differ from ours. Mainly, these reviews had less RCTs of antipsychotic drugs available, but included more RCTs of antidepressants since these drugs have been tested in mixed samples that were not includable in this review (if less than 70% of participants had a diagnosis of BPD, see Types of studies). Outcomes were, by and large, comparable to those of our review. All three reviews conducted meta-analyses across classes of drugs, i.e. effect estimates referring to a certain class of drugs (any antipsychotic, any antidepressant, or any mood stabiliser) were pooled. In this review, study effects were only pooled if referring to the same substance.

Both reviews report several findings of effectiveness for antidepressants. This differs from our findings that are only based on RCTs conducted in study samples of more than 70% BPD patients, and were not derived from accumulation of findings from different (antidepressant) substances.

Guidelines

This systematic review is not a guideline, which provides treatment recommendations. It is meant to help providers, practitioners and patients make informed decisions. However, we will now comment on the main guidelines that give recommendations for pharmacotherapy treatment of BPD in light of the results of this systematic review.

The American Psychiatric Association Practice Guidelines (APA 2001; updated in 2005, APA 2005) are commonly cited when recommending pharmacological treatment strategies for BPD. However, these are based on literature searches covering the literature up to 1998. Since then, 20 RCTs have been published, investigating mood stabilisers (valproate semisodium, lamotrigine, topiramate), antidepressants (fluvoxamine, fluoxetine), second-generation antipsychotics (aripiprazole, olanzapine, ziprasidone), and omega-3 fatty acids.

Taking the findings of this review into account with regard to the APA guidelines, some differences are apparent: The up-to-date RCT evidence presented here does not support the recommendation of SSRIs as first-line treatment for affective dysregulation and impulsive-behavioural dyscontrol symptoms. Instead, beneficial effects were found for mood stabilisers (topiramate, valproate semisodium, lamotrigine) and second-generation antipsychotics (aripiprazole, olanzapine) for affective dysregulative symptoms. Beneficial effects indicating a reduction of impulsive-behavioural dyscontrol symptoms are available for mood stabilisers (topiramate, lamotrigine) or second-generation antipsychotics (aripiprazole). The APA guidelines recommend low-dose antipsychotics in general for the treatment of cognitive-perceptual symptoms, whereas our findings support the use of SGA (aripirazole, olanzapine) in particular. This development, a shift towards second-generation antipsychotics, has been foreshadowed by John M. Oldham in his guideline watch of 2005 (APA 2005APA 2005), butto our knowledge, the original guideline recommendations have not been modified since.

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Personality Disorders (Herpertz 2007), that are based upon RCTs, open trials and individual clinical experiences, refer to all evidence that was identified in MEDLINE searches up to June 2007. Although their aim was to grade the evidence for the use of drugs in BPD treatment, and to give recommendations based not only on RCT but also lower-level evidence, they conclude that there is no evidence at either level of evidence that any drug improves BPD psychopathology in general. In addition, they did not find any beneficial evidence for the use of a the combination of several drugs. In contrast to this review, the WFSBP guidelines conclude that SSRIs "are best shown to influence emotional dysregulation such as depressive mood, anxiety and mood swings and [...] appear to extend the improvement of comorbid conditions of mood and anxiety disorders." (Herpertz 2007, p. 214). This recommendation is not corroborated by the RCT evidence, as investigated in this review. Additionally, some trials were included in the WFSBP guidelines as randomised controlled trials, that were not included in this review due to stricter inclusion criteria (see Criteria for considering studies for this review and Excluded studies).

The NICE guideline on treatment and management of BPD (NICE 2009) is based on a similar pool of RCTs, even if the NICE literature searches were last updated in May 2008 (NICE 2009, p. 56). The guideline developers recommend that "Drug treatment should not be used specifically for borderline personality disorder or for the individual symptoms or behaviour associated with the disorder (for example, repeated self-harm, marked emotional instability, risk-taking behaviour and transient psychotic symp-

toms)." (NICE 2009, p. 297). This seems somehow contradictory to the findings of this review. However, the scope of NICE and this Cochrane Collaboration review differ in asking different questions and using different means and methods to answer them. In relation to the question or topic, this Cochrane review aims at reviewing all of the available valid RCT evidence concerning pharmacotherapy of BPD treatment, whereas NICE aims at providing specific recommendations for a defined clinical setting, with pharmacotherapy being only one component within a comprehensive framework of possible health care provisions. Regarding methods, NICE considers somewhat different sources of evidence and applies additional criteria to weigh the costs and benefits of treatments ("NICE has always been focused on providing guidance on the most effective way to use NHS resources", NICE 2010) and it is consensus-based. In contrast, the aim of this review is, according to Cochrane Collaboration standards, "to present information, rather than to offer advice" (Higgins 2008, p. 67).

AUTHORS' CONCLUSIONS

Implications for practice

The current RCT evidence supporting the use of pharmacotherapy for BPD is very sparse when compared to its widespread usage. Despite the remarkable growth in RCT evidence (this review includes 18 more RCTs than its previous version of 2006, with 9 different substances under test), the conclusion that pharmacotherapy in BPD "is not based on good evidence from trials" (Binks 2006, p. 19) still stands. There are only a few study results per comparison, with small numbers of included participants. However, it is important to remember that no evidence of an effect is not evidence of no effect. Current findings from RCTs presented in this review are not robust and can easily be changed by future research.

The findings suggest there is support for the use of second-generation antipsychotics, mood stabilisers, and omega-3 fatty acids, but these require replication since most effect estimates were based on single study effects. The small amount of available information for individual comparisons indicated marginal effects for first-generation antipsychotics and antidepressants.

Notably, avoidance of abandonment, chronic feelings of emptiness, identity disturbance, and dissociation were not found to be affected significantly by any drug. This finding may be the result of the use of non-BPD specific assessment instruments that do not reproduce these very specific outcomes, but it also reflects that these symptoms are broadly not regarded treatable by pharmacotherapeutic interventions and remain subject to non-pharmaceutical treatments such as psychotherapy.

It is important to consider the adverse effects for these interventions. Most trials did not provide detailed data of adverse effects, but these can be assumed to be similar to those experienced by patients with other conditions. However, the data available suggest an increase in self-harming behaviour when using olanzapine. In addition, toxic effects in case of overdosing (e.g. TCA antidepressants) and the potential for misuse or substance dependence (e.g. hypnotics and sedatives) need special attention in BPD treatment. In the presence of a comorbid eating disorder, possible effects on body weight changes (especially weight gain by olanzapine treatment and weight loss by topiramate treatment) should be taken into accountand discussed between the treating physician and the patient ("shared decision making").

Currently, there is no evidence from RCTs that any drug reduces overall BPD severity, but there are distinct pathology facets. Therefore, pharmacotherapeutic treatment of BPD should be targeted at defined symptoms. Drug treatment should last a sufficient period of time (according to pharmacokinetic and dynamic properties of a certain substance) to judge if there are any benefits, and should be stopped or changed if there are none. Polypharmacy is not supported by the up-to-date evidence and should be avoided wherever possible.

As discussed above, the evidence is not robust. The studies may not adequately reflect several characteristics of clinical settings (among others, patients' characteristics and duration of interventions and observation periods). Further research is urgently needed to provide reliable recommendations. Furthermore, there are some difficulties stemming from the polythetic nature of BPD. Different patients with BPD are likely to experience different facets of the disorder, and clinicians working with these patients are acquainted with different subtypes. The question "What works for whom?" remains broadly unanswered. Consequently, there is little consensus among researchers about a common battery of outcome variables and measures, even for primary studies testing the same drugs with putatively the same treatment targets and effects. Thus, we have a fragmentary view on drug effects, and it remains uncertain how the modulation of one symptom affects another.

People with BPD and their carers should lobby for and facilitate good research.

Implications for research

In recent years, a shift of attention in BPD treatment research has been observed towards SGAs and mood stabilisers, which may be a consequence of study sponsoring by pharmaceutical companies.

Some other classes of drugs have been paid much less attention to than their actual importance in clinical settings suggests. For example, antidepressants, especially SSRIs, play a major role in everyday practice but currently only three placebo-controlled RCTs exist that tested SSRIs in BPD. These drugs urgently need further attention in future placebo-controlled RCTs of BPD treatment. However, replicative studies for all comparisons would be desirable in order to enhance the robustness of findings. On the

other hand, placebo-controlled RCTs testing different mood stabilisers (such as oxcarbazepine) and SGAs (e.g. clozapine, quetiapine, risperidone) that have lately been investigated in several non-randomised studies with promising results would be of interest. Currently, there is no RCT evidence-based "gold standard", so any future research endeavour should comprise a placebo condition. Longer observation periods would be sensible, this would enhance external validity and the applicability of findings to primary care settings. Additionally, patients with comorbid axis-I disorders should not be excluded, as psychiatric comorbidities are common in BPD patients. Another point for future research may be the update of popular algorithms to follow in this patient group, e.g. the "Soloff-algorithm" (Soloff 1998Soloff 1998) or the APA guidelines algorithm (Oldham 2004Oldham 2004).

There is a huge heterogeneity of outcome variables and assessment instruments. A consensus on a minimum set of therapy outcome variables that are most likely to be of interest for any BPD patient would be desirable. Outcome assessment should be more specific and sensitive to BPD relevant pathology. For example, psychotic pathology should be assessed in terms of BPD relevant symptoms, i.e. stress-related paranoid ideation. Fortunately, several assessment instruments have been developed lately to reflect BPD core pathology as described precisely by the DSM-IV criteria (e.g. the BPDSI scale by Arntz 2003, the CGI-BPD scale by Perez 2007, or the ZAN-BPD scale by Zanarini 2003a). However, some DSM-IV BPD criteria embrace several symptoms, e.g. the criterion of "stress-related paranoid ideation OR dissociation". The possibility of more differentiated outcome assessment may stimulate further research on drugs that may affect BPD core symptoms but have been neglected in the existing RCTs. In particular, drugs targeting affective instability, an important hallmark of BPD pathology, would be of interest. Outcome assessment should also embrace a thorough, standardized assessment of adverse events. Spontaneous reporting of patients may not be as valid and comprehensive as would be desirable.

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Zanarini MC, Frankenburg FR, Reich DB, Silk KR, Hudson JI, McSweeney LB. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. *American Journal of Psychiatry* 2007;**164**(6):929–35.

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Lieb K, Völlm B, Rücker G, Timmer A, Stoffers JM. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *British Journal of Psychiatry* 2010;**196**:4–12.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bogenschutz 2004

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double, no further details Duration: 12 weeks (patients had to be free of mood stabilisers, antipsychotics, benzodiazepines, and antidepressants for at least 2 weeks prior to participation) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II) Age: Mean 32.6 years (SD = 10.3) Sex: 25 F, 15 M Exclusions: Schizophrenia, schizoaffective disorder, bipolar affective disorder, current major depressive episode, psychotic disorder due to substance or general medical condition, substance dependence not in full or partial remission, suicide attempts in past 6 months, having current suicidal intent or definite plan, pregnancy, neurologic impairment
Interventions	1. Olanzapine: flexible dose (2.5-20 mg/day), mean dose at endpoint: 6.9 mg/day (SD = 3.2) N = 20* 2. Placebo: no further details, mean pseudo-dose at endpoint: 10.2 mg/day (SD = 5.3) N = 20* Concomitant psychotherapy: Allowed to continue if initiated more than 3 months prior to randomization Concomitant pharmacotherapy: Medication for stable, chronic medical conditions such as hypertension
Outcomes	Avoidance of abandonment: CGI-BPD-abandonment Interpersonal problems: CGI-BPD-unstable interpersonal relationships Identity disturbance: CGI-BPD-identity disturbance Impulsivity: CGI-BPD-impulsivity, OAS-M-aggression Suicidal ideation: CGI-BPD-recurrent suicidal ideation Affective instability: CGI-BPD-affective instability Feelings of emptiness: CGI-BPD-chronic feelings of emptiness Anger: CGI-BPD-inappropriate anger, AIAQ Dissociative symptoms: CGI-BPD-transient paranoia or dissociation Anxiety: HARS General psychiatric pathology: SCL-90 Mental health status: CGI Attrition Adverse effects: weight
Notes	*as randomised
Risk of bias	

Bogenschutz 2004 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Patients were randomly assigned in equal numbers" (Bogenschutz 2004, p. 105)
Allocation concealment?	Unclear	Comment: No information provided
Blinding? self-rated outcomes	Unclear	Quote: "double-blind trial", "pseudo-dose [...] for patients receiving placebo" (Bogenschutz 2004, p. 105)
Blinding? observer-rated outcomes	Unclear	Quote: "double-blind trial", "pseudo-dose [...] for patients receiving placebo" (Bogenschutz 2004, p. 105) Comment: No information provided on who actually adjusted the dose and if this person was blind to the patients' allocation
Incomplete outcome data addressed? All outcomes	Unclear	Comment: "evaluable patients" refers to all patients remaining at least 2 weeks in the study, i.e. who attended both baseline and preliminary assessment after two weeks; reasons for early termination specified (Bogenschutz 2004, p.106). However, 2 patients dropped out of the olanzapine group due to "violation of protocol" (Bogenschutz 2004, p. 106) Of the 40 patients enrolled, 23 completed the full 12 weeks of the trial (10 in olanzapine group, 13 in placebo group) Reasons for early termination: Lost to follow-up: 2 in the olanzapine group, 5 in the placebo group Lack of efficacy: 2/2 Weight gain: 2/0 Sedation: 2/0 Violation of protocol: 2/0 Continuous data based on LOCF of patients remaining at least 2 weeks in the study dichotomous data based on ITT sample
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "No other psychotropic medications could be taken during the study

Bogenschutz 2004 (*Continued*)

		or in the 2 weeks prior to the study." (Bogenschutz 2004, p. 105)
Bias due to sponsoring improbable?	No	Quote: "Supported by a grant from Eli Lilly and Co, Indianalpolis, Ind." (Bogenschutz 2004, p. 104)

De la Fuente 1994

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double. (One clinician was blind to drug treatment and performed all clinical and psychometric assessments, the other one was not blind to drug treatment and correctly adjusted the plasma levels of carbamazepine and asked for adverse side effects. Patients were instructed not to communicate side effects to the blind clinician) Duration: 32 days (after at least 10 days psychotropic drug washout; 15 days for TCAs and MAOIs, no patient had taken neuroleptics in the 2-month period before the study) Setting: Inpatients
Participants	Diagnosis: BPD (DSM-III-R; DIB) Age: Mean 32.7 years (range 22-45) Sex: 14 F, 6 M Exclusions: DSM-III-R axis I disturbances (not excluded: patients who were depressed for less than 2 weeks), inability to stop alcohol or psychoactive substances, suspected poor treatment compliance, standard physical or neurological examinations abnormal, perturbed standard biological blood tests, perturbed electrocardiogram, positive history for epilepsy or standard traits for epilepsy, antecedents of encephalitis or cranial trauma
Interventions	1. Carbamazepine: therapeutic range of blood drug levels required for the management of epileptic and affectively ill patients; averages were continuously between 6.44-7.07 micrograms/mL for carbamazepine and 1.07-1.24 micrograms/mL for 10.11-epoxycarbamazepine) N = 10* 2. Placebo: no further details N = 10* Concomitant psychotherapy: Supportive atheoretical psychotherapy was administered to all patients Concomitant pharmacotherapy: No further details
Outcomes	Interpersonal problems: SCL-90-INT Impulsivity: Acting-out scale Anger: SCL-90-HOS Psychotic symptoms: BPRS, SCL-90-PSY, SCL-90-PAR Depression: HDRS-24 Anxiety: SCL-90-ANX General psychiatric pathology: GAS, SCL-90-PST Attrition Adverse effects: asked for by the non-blind clinician

De la Fuente 1994 (*Continued*)

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Of the 20 patients enrolled in the trial, we randomized 10 into the CBZ [carbamazepine] group and 10 received PLC [placebo]" (De la Fuente 1994, p. 481)
Allocation concealment?	Unclear	Quote: "The study was carried out by two clinicians. One of them [...] was blind and performed all the clinical and psychometric assessments. The other one [...] who was not blind to the drug treatment, correctly adjusted the plasma levels of CBZ and asked for adverse side effects." (De la Fuente 1994 p. 480) Comment: Unclear, who exactly enrolled patients.
Blinding? self-rated outcomes	Unclear	Quote (Eur Neuropsychopharmacol, 1994, 4): "[...] active or placebo treatment. We administered it in a single daily dose at 10 p.m. [...] The study was carried out by two clinicians. One of them [...] was blind [...]. The other one who was not blind to the drug treatment, correctly adjusted the plasma levels of CBZ and asked for adverse side effects." (p. 480) Comment: Unclear, if opaque capsules were used, and if a pseudo-adjustment of the placebo dose was done
Blinding? observer-rated outcomes	Yes	Quote: "The study was carried out by two clinicians. One of them [...] was blind to the drug treatment and performed all the clinical and psychometric assessments. [...] We instructed the patients to not communicate side effects to the blind clinician." (De la Fuente 1994, p. 480)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Of the 20 patients enrolled in the trial, we randomized 10 into the CBZ group and 10 received PLC. [...] Two patients receiving CBZ dropped out. [...] No patient on PLC dropped out." (De la

De la Fuente 1994 (*Continued*)

		Fuente 1994, p. 481). Reasons for early termination: Dramatic increase in frequency and intensity of aggression (against self and others) : 2 in carbamazepine group, 0 in placebo group Comment: Reasons for early termination specified (De la Fuente 1994, p.481). However, it remains unclear if the reported continuous outcomes confer to LOCF analyses. We decided to use the same numbers of patients for which dichotomous outcomes were reported. For dichotomous outcomes, lacking numbers of patients were imputed as having the unfavourable results.
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Patients underwent a psychotropic washout period of at least 10 days before the beginning of the treatment period (15 days for tricyclic antidepressants and monoamine oxidase inhibitor agents) . No patient had taken neuroleptics in the 2-month period before the study." (De la Fuente 1994, p. 480)
Bias due to sponsoring improbable?	Unclear	No details about funding or sponsoring provided.

Frankenburg 2002

Methods	Design: RCT Allocation: Randomised in a 2:1 manner; tablets were supplied in numbered bottles containing drug or placebo as determined by a prearranged random number sequence Blinding: Double-blind; one investigator was given either real drug blood levels or sham levels (in case of placebo) and adjusted the dose according to perceived response, reported or sham level, and side effects Duration: 6 months Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV; DIPD-IV borderline module) + bipolar II disorder (DSM-IV) Age: Valproate semisodium group: mean age 27.3 (SD 7.4), placebo group: mean age 26.4 (SD 7.3) Sex: 30 F Exclusions: Acutely suicidal patients (i.e. having clear-cut and pressing intent to commit

	suicide in near future); actively abusing alcohol or drugs; current criteria for major depressive episode or hypomanic episode met; current or lifetime schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, bipolar I disorder; patients formerly been treated with valproate semisodium; subjects who were pregnant, breastfeeding or not using reliable forms of contraception; medically ill, seizure disorder
Interventions	1. Valproate semisodium: Adjusted to achieve a serum valproate semisodium level of between 50 and 100 mg/L; actual average dose: 850 mg/day (SD 249) or 3.4 tablets/day (SD .9) N = 20* 2. Placebo: tablets; actual average dose: 2.6 tablets/day (SD .5) N = 10* Concomitant pharmacotherapy: No other psychotropic medication allowed Concomitant psychotherapy: No patient was in psychotherapy
Outcomes	Interpersonal problems: SCL-90-INT Impulsivity: MOAS Anger: SCL-90-HOS Depression: SCL-90-DEP Attrition Adverse effects: weight, menstrual changes, tremors, diarrhea, hair loss, increase in hepatic transaminases, thrombocytopenia
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "Prearranged random number sequence" (p. 443)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered bottles containing drug or placebo as determined by a prearranged random number sequence" (p.443)
Blinding? self-rated outcomes	Yes	Quote: "Tablets were supplied in numbered bottles [...] Each tablet contained either 250 mg of valproate semisodium or matching inert placebo. [...] One of the investigators [...] was given either the real or a sham level (if the subject was receiving placebo). This same investigator met with the subjects for [...] medication checks and adjusted the dose according to perceived response, reported or sham level, and side effects.

Frankenburg 2002 (*Continued*)

Blinding? observer-rated outcomes	Unclear	Comment: No information given on who exactly assessed outcomes.
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Endpoint values [...] are based on last observation carried forward." (p. 444) Comment: reasons for early termination specified (p.444). For dichotomous outcomes, lacking numbers of patients were imputed as having the unfavourable result. Of the 30 patients enrolled, 11 completed the full 24 weeks of the trial (7 in valproate semisodium group, 4 in placebo group) Reasons for early termination: Lost to follow-up: 9 in the valproate semisodium group, 3 in the placebo group Moved out of the area: 1/0 Inability to use reliable forms of contraception: 1/0 Withdrawal of consent: 1/0 Diarrhea and tremors: 1/0 Development of a major depressive episode: 0/2 Hair loss: 0/1
Free of selective reporting?	Unclear	Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "No other psychotropic medication was allowed during this study." (p. 443)
Bias due to sponsoring improbable?	No	Quote: "Supported by a grant from Abbott Laboratories, Chicago, Ill." (p. 442)

Goldberg 1986

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double Duration: 12 weeks (after 1 week placebo washout) Setting: Outpatient
Participants	Diagnosis: BPD and/or schizotypal personality disorder (DSM-III; SIB) and having at least one psychotic symptom Age: Mean 32 years (no SD given) Sex: 29 F, 21 M Exclusions: Current alcoholism or drug addiction, schizophrenia, mania, melancholia, severe hepatic, renal, or cardiovascular disease, organic brain syndrome, mental retardation, history of epilepsy or seizures, glaucoma, severe hypertensive or hypotensive car-

Goldberg 1986 (*Continued*)

	diovascular disease, severe metabolic disorders
Interventions	1. Thiothixene: mean final dose 8.67 mg/day (range 2 mg/day - 35 mg/day) N = 24* 2. Placebo: no further details, mean pseudo-dose at endpoint 26.38 mg/day (not further specified) N = 26* Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Patients had to pass one week placebo washout; no further details
Outcomes	BPD severity: SIB-borderline score Interpersonal problems: HSCL-INT Anger: HSCL-HOS Psychotic symptoms: SIB-psychotic Depression: HSCL-DEP Mental health status: GAS Attrition Adverse effects
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Randomly allocated to thiothixene or placebo" (p. 681)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Yes	Quote: "Both agents were provided in identical-appearing capsules containing 5 mg of thiothixene hydrochloride or an equivalent amount of lactose for placebo. The initial dose for all patients was one capsule [...] and on each succeeding visit the dose was increased by one capsule unless side-effects or marked improvement intervened. A maximum dose of 40 mg, or eight capsules, was to be allowed [...]. (p. 682)
Blinding? observer-rated outcomes	Yes	Quote: "Both agents were provided in identical-appearing capsules containing 5 mg of thiothixene hydrochloride or an equivalent amount of lactose for placebo. The initial dose for all patients was one capsule [...] and on each succeeding visit the dose was increased by one capsule unless side-effects or

Goldberg 1986 (*Continued*)

		marked improvement intervened. A maximum dose of 40 mg, or eight capsules, was to be allowed [...]. (p. 682) Comment: Trial described as "double-blind" (p. 681)
Incomplete outcome data addressed? All outcomes	Yes	Quote: "Patients who terminated their participation early were assessed at that point and those assessments were taken as their endpoints." (p. 682) Of the 50 patients enrolled, 40 completed treatment (17 in thiothixene group, 23 in placebo group) reasons for early termination: Adverse effects: 7 in thiothixene group, 0 in placebo group Lack of efficacy: 0/3 Continuous data based on LOCF
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "One-week placebo washout" (p. 681)
Bias due to sponsoring improbable?	Unclear	No details about funding or sponsoring provided

Hallahan 2007

Methods	Design: RCT Allocation: Randomised, according to computer-generated list Blinding: Double-blind; an independent colleague dispensed identically looking capsules according to computer-generated list, code was only revealed after completion of data collection Duration: 12 weeks Setting: Outpatient
Participants	Diagnosis: Patients with recurrent self-harm, recruited at an accident and emergency department where they had presented acutely with self-harm; additionally, participants had to have a lifetime history of at least one other self-harm episode. Actually, 71% of all participants satisfied DSM-IV BPD criteria as assessed by SCID-II Age: Mean 30.6 years Sex: 17 M, 32 F Exclusions: Current addiction, substance misuse, psychosis, eating disorder, dyslipidaemia, treatment, diet or illness known to interfere with study drug, weight loss > 10% during previous 3 months, taking supplements containing omega-3 fatty acids of consuming fish more than once per week, changes to, or introduction of psychotropic

	medication during previous 6 weeks pregnancy
Interventions	1. Omega-3 fatty acid: 1.2 g/day of eicosapentaenoic acid (E-EPA)+ 0.9 g/day of docosahexaenoic acid (DHA) N = 22* 2.Placebo: capsules contained 99% corn oil and a 1% E-EPA + DHA mixture, ensuring blindness by also causing 'fishy breath', the most frequent side-effect of the active drug N = 27* Concomitant psychotherapy: Patients actually receiving psychotherapy were not eligible for study participation Concomitant pharmacotherapy: Patients could continue to receive standard psychiatric care and had changes to their psychotropic medication as prescribed (53.1% of participants actually did) . Patients with changes to or introduction of psychotropic medication during the 6 weeks prior to screening were not eligible.
Outcomes	Suicidal ideation: Number of patients with OAS-M-suicidality subscale score of 1 or higher, indication at least slight suicidal tendencies Self-mutilating behaviour: Number of patients with episodes of self-harm during treatment Depression: Number of patients with at least 50% and 70% reduction of depressive pathology as assessed by both BDI and Ham-D Attrition: Number of non-completers
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "computer-generated list" (p. 119)
Allocation concealment?	Yes	Quote: "An independent colleague dispensed either active or placebo capsules according to a computer-generated list."
Blinding? self-rated outcomes	Yes	Quote: "Participants were prescribed four identical capsules of either active agent or placebo [...] Placebo ensured a degree of equality in the incidence of 'fishy breath', the most frequent side-effect of taking active treatment." (p. 119)
Blinding? observer-rated outcomes	Yes	Quote: "identical capsules [...] Placebo ensured a degree of equality in the incidence of 'fishy breath' [...] An independent colleague dispensed [...] capsules according to a computer-generated list. The code was only revealed to the researchers once data collection was complete." (p. 119)

Hallahan 2007 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Comment: LOCF used, reasons for early termination specified (p. 120) Of the 49 patients enrolled, 39 completed treatment (19 of the 22 allocated to active treatment, 20 of the 27 allocated to placebo) Reasons for early termination: Left district: 1 in active group, 2 in placebo group Lost to follow-up: 2 in active group, 2 in placebo group Admitted to psychiatric hospital: 0 in active group, 2 in placebo group Refused to continue treatment: 0 in active group, 1 in placebo group Dichotomous outcomes calculated on basis of the ITT sample
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	No	Quote: "Patients had changes to their psychotropic medication as prescribed by their treating agency." (p. 118)
Bias due to sponsoring improbable?	Yes	Quote: "Pronova (now Epax) AS, Lysaker, Norway, provided the active preparation and placebo but were not otherwise involved in the study." (p. 118) Quote: "B.H. [i.e. first author] received salary support from the Department of Psychiatry, University of Illinois at Chicago, USA." (p. 122)

Hollander 2001

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind; treating psychiatrist was kept blind to patient medication, blood valproate levels were read and dose adjustments to both valproate semisodium and placebo were determined by a psychiatrist not seeing patients for this study Duration: 10 weeks (no washout reported) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV; SCID-II) Age: Mean 38.6 years (SD = 10.37, range 18 - 62) Sex: 11 F, 10 M Exclusions: Current suicidal ideation, current substance abuse, current major depression,

Hollander 2001 (*Continued*)

	bipolar disorder type I or II, psychotic disorders, medical or neurologic illness, pregnancy
Interventions	1. Valproate semisodium: dose sufficient to maintain blood valproate level at 80 micrograms/mL or the highest tolerated dose; mean endpoint blood valproate level 64.57 micrograms/mL (SD 15.21, range 47-85 micrograms/mL) N = 12** 2.Placebo: no further details N = 4** Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Not specified
Outcomes	Impulsivity: AQ, OAS-M-aggression Anger: OAS-M-irritability Suicidal behaviour: OAS-M-suicidality Depression: BDI Mental health status: non-responders (CGI-I score of 3 or more) Attrition
Notes	**Initially 21 subjects entered the study, only 16 were randomised to a treatment group without giving reasons Continuous outcomes based on ITT (LOCF) Of the 16 patients randomised, 6 completed treatment (6 in valproate semisodium group, 0 in placebo group) Reasons for early termination: All patients dropped out owing to either lack of efficacy or impulsive decisions, none dropped out owing to side effects

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Patients were randomly assigned [...] at an approximate ratio of 2:1" (p. 201)
Allocation concealment?	No	Quote: "Although the planned patient assignment ratio was 2:1 [...], the ratio was actually 3:1" (p.202) Comment: First, the authors say that there was an approximate ratio of 2:1 randomisation was planned. However, it remains unclear why the actual ratio turned out to be 3:1, even if taking the small number (16) of participants into account. A 2:1 ratio assignment would have been feasible.
Blinding? self-rated outcomes	Unclear	Quote: "The treating psychiatrist was kept blind to patient medication, blood valproate levels were read and dose adjustments to both valproate semisodium and

		placebo were determined by a psychiatrist not seeing patients for this study." (p. 201) Comment: No information given if opaque capsules were used, and if the placebo pseudo-dose was also "adjusted".
Blinding? observer-rated outcomes	Unclear	Quote: "clinician-rated outcome measures [...] based on the average of the ratings of the treating psychiatrist and independent evaulator (a psychologist blind to side effects as well as to medication group)" (p.201) Comment: No information given on who exactly assessed observer-rated outcomes.
Incomplete outcome data addressed? All outcomes	No	Quote: "Patients taking valproate semisodium had a 50% dropout rate [...] versus 100% dropout in the placebo group. [...] No patients dropped out owing to side effects; all dropped out owing to either lack of efficacy or impulsive decisions. [...]" (p.201) Comment: LOCF used (p. 202) Initially 21 subjects entered the study, only 16 were randomised to a treatment group without giving reasons Of the 16 patients randomised, 6 completed treatment (6 in divalproex group, 0 in placebo group) reasons for early termination: "No patients dropped out owing to side effects; all dropped out owing to either lack of efficacy or impulsive decisions. [...]" (p.201)
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Unclear	Comment: Not specified if there was a washout-period preceding the trial or if concomitant psychotropic medication was allowed
Bias due to sponsoring improbable?	No	"Supported in part by grants from the National Institute of Mental Health (1 RO3 MH58168-01A1), Richville, Md. (Dr. Hollander); Abbott Laboratories, Abbott Park, Ill. (Dr. Hollander); the National Center for Research Resources, National

		Institutes of Health (5 MO1 RR00071) , Rockville, Md., for the Mount Sinai General Clinical Research Center; and the Seaver Foundation and the PBO Foundation, New York, N.Y." (p. 199)

Leone 1982

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Drugs were supplied in identical opaque capsules Duration: 6 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-III, no further details) Age: Loxapine group: mean 29.5 years (range 16-54 years), chlorpromazine group: mean 32 years (range 16-59 years) Sex: 48 F, 32 M Exclusions: Using sedatives or tranquilisers, having been treated with psychotropic drugs within 48 hours of beginning treatment with study drugs, allergy/hypersensitivity to study drugs, organic brain syndrome, mental retardation, severe medical disease
Interventions	1. Loxapine: capsules of 5 mg, starting dose one or two capsules daily, increased based on symptom severity and tolerance; maximum dose 12 capsules/d; mean final dose 13.5 mg/day, overall mean daily dose 14.4 mg N = 40* 2. Chlorpromazine: capsules of 50 mg, starting dose one or two capsules daily, increased based on symptom severity and tolerance; maximum dose 12 capsules daily; mean final dose105 mg/day, overall mean daily dose 110 mg N = 40* Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Patients did not receive any other psychotropic medication during the study; nighttime sedatives were limited to flurazepam and chloral hydrate
Outcomes	BPD severity Affective instability: POMS Psychotic symptoms: BPRS Mental health status: CGI, Systematic Nurses' Observation of Psychopathology (SNOOP) Attrition Adverse effects: Recorded upon appearance in terms of data of onset, intensity, duration, and any remedial action Unable to use outcome data (except for attrition)
Notes	*As randomised

Risk of bias

Leone 1982 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Matched groups [...] Subjects [...] were selected randomly to receive loxapine or chlorpromazine. [...] There were 24 women and 16 men in each treatment group." (p. 148) Comment: probably matching procedure used
Allocation concealment?	Unclear	Comment: No information given.
Blinding? self-rated outcomes	Yes	Quote: "drugs were supplied in identical opaque capsules" (p. 148) Comment: No self-rated outcomes used.
Blinding? observer-rated outcomes	Unclear	Comment: No information given. Within this review, only the outcomes of attrition and adverse effects, that were "recorded upon appearance" (p. 148), were used. For these, the review authors assume the risk of bias as moderately.
Incomplete outcome data addressed? All outcomes	Yes	Continuous outcomes based on available cases Of the 80 patients enrolled, 69 completed at least 3 weeks of treatment and were included (34 in loxapine group, 35 in placebo group) Reasons for early termination: Did not follow study procedures: 4 in loxapine group, 4 in chlorpromazine group Had to be admitted to hospital within 3 days: 2 in loxapine group, 1 in chlorpromazine group Comment: Only dichotomous outcomes used here, for which dropped-out patients were imputed as having the negative outcome.
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Unclear	Quote: "Patients did not receive any other psychotropic medication during the study; nighttime sedatives were limited to flurazepam and chloral hydrate." (p. 148) Comment: Actually, patient could thus receive concomitant sedatives, but it is not

Leone 1982 (*Continued*)

		specified how many did.
Bias due to sponsoring improbable?	No	Quote: "This study was supported by a grant from Lederle Laboratories, Pear River, New York." (p. 148)

Linehan 2008

Methods	Design: RCT Allocation: Content of tablets was determined by a random number sequence Blinding: Patients, psychotherapists, pharmacotherapist, and assessment interviewers were kept naive to medication assignment Duration: 24 weeks, last assessment after week 21, however Setting: Outpatient
Participants	Diagnosis: BPD according to DSM-IV (SCID-II, PDE) + BPD criterion for inappropriate anger met + score of 6 or higher on the irritability scale of the OAS-M Age: Overall mean age 36.8 years (SD=9.0) Sex: 24 F Exclusions: Episode of self-inflicted self-injury including suicide attempts during 8 weeks prior to screening, current diagnosis of schizophrenia, bipolar I disorder, schizoaffective disorder, major depressive disorder with psychotic features or other psychotic disorder, substance dependence during last 6 months, mental retardation, seizure disorder, pregnant women or planning to be, breastfeeding
Interventions	1. DBT + olanzapine (allowed dosage range: 2.5 to 15 mg/day; mean daily dose 4.46 mg/day, SD 1.16) N = 12* 2. DBT + placebo (dose was adjusted in response to perceived response and side effects, no further details) N = 12* Data refer to the intention to treat sample Concomitant psychotherapy: All participants received DBT Concomitant pharmacotherapy: n.s.
Outcomes	Suicidal ideation: Number of patients with high suicidality score on the OAS-M suicidality subscale Self-mutilating behaviour: number of patients with self-injury Depression: Ham-D Attrition Adverse effects: Weight gain (lb), remaining data on adverse effects not usable
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Linehan 2008 (*Continued*)

Adequate sequence generation?	Yes	Quote: "random number sequence" (p. e2)
Allocation concealment?	Yes	Quote: "each tablet contained either 5 mg of olanzapine or matching inert placebo as determined by a random number sequence" (p. e2)
Blinding? self-rated outcomes	Yes	Quote: "Patients, psychotherapists, pharmacotherapist, and assessment interviewers were kept naive to medication assignment. (p. e2)
Blinding? observer-rated outcomes	Yes	Quote: "Patients, psychotherapists, pharmacotherapist, and assessment interviewers were kept naive to medication assignment. At the end of the study, the pharmacotherapist and interviewers were unable to guess group assignment above chance." (p. e2)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Outcomes were intent-to-treat analyses" (p. e3) Comment: Reasons for early termination specified (p. e4); dropped-out patients were imputed as having the negative outcome
Free of selective reporting?	Unclear	Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Unclear	Quote: "To enhance compliance, tablets were given in [...] prescription bottles programmed to sound a sequence of alarms when medications were due, terminating only when the medication top was removed." Comment: Compliance was thus controlled for Comment: Not specified if concomitant medication was allowed or not
Bias due to sponsoring improbable?	No	Quote: This research was supported by a grant from Eli Lilly and Co., Protocol F1D-US-X173, to Dr. Linehan; by Remind Rx Medication Compliance Systems; and by a contribution of electronic pill bottles from IBV Technologies, Seattle, Wash. [...] Dr. Linehan is a consultant for, has received grant/research support and honoraria from, and is a member of the speakers/advisory

		board fro Eli Lilly. Drs. McDavid, Brown, Sayrs, and Gallop report no additional financial or other relationships relevant to the subject of this article." (p. 999)

Loew 2006

Methods	Design: RCT Allocation: Randomisation was carried out confidentially by the clinic administration, tablets were supplied in numbered boxes Blinding: Double-blind, blind medication which constituted either the active drug or placebo Duration: 10 weeks Setting: Outpatient
Participants	Diagnosis: BPD (SCID-II) Age: Mean age active drug group: 24.9 (SD = 5.3), placebo group 25.6 (SD = 5.7) Sex: 56 F Exclusions: Currently suicidal patients, abusing alcohol or drugs, schizophrenia, severe somatic illness, current use of topiramate or other psychotropic medication, or psychotherapy
Interventions	1. Topiramate: 200 mg/day N = 28* 2. Placebo: analogous pseudo-dose N = 28* Concomitant psychotherapy: Not allowed Concomitant pharmacotherapy: Any other psychotropic medication not allowed
Outcomes	Interpersonal problems: SCL-90-R-INT Anger: SCL-90-R-HOS Psychotic symptoms: SCL-90-R-PAR, SCL-90-R-PSY Depression: SCL-90-R-DEP Anxiety: SCL-90-R-ANX General psychiatric pathology: SCL-90-R-GSI Attrition Adverse effects: non-structured questionnaire
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Randomization was carried out confidentially by the clinic administration" (Loew 2006, p. 63)

Loew 2006 (*Continued*)

Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered boxes." (Loew 2006, p. 63)
Blinding? self-rated outcomes	Yes	Quote: "blinded medication" (Loew 2006, p. 63), "subjects [...] were blinded regarding [...] assignment" (Loew 2006, p. 63)
Blinding? observer-rated outcomes	Yes	Quote: "blinded medication" (Loew 2006, p. 63), "clinicians were blinded regarding [...] assignment (Loew 2006, p. 63)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Fifty-nine subjects were eligible to take part in the study [...] 56 patients were required [...] randomization was carried out [...] with a 1:1 assignment to the active drug (N = 28) and placebo (N = 28)" (Loew 2006, p. 63) Of the 56 patients enrolled, 52 completed treatment (27 in topiramate group, 25 in placebo group) reasons for early termination: Absent more than twice for weekly evaluation: 1 in the topiramate group, 3 in the placebo group LOCF used, reasons for early termination specified (Loew 2006, p. 63) Comment: Not clear, why or how the 56 participants were finally chosen out of the 59 potential participants
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "exclusion criteria included [...] the current use of topiramate or other psychotropic medication." (p. 62)
Bias due to sponsoring improbable?	Unclear	Quote: "The study was planned and conducted independent[ly] of any institutional influence and approved by the clinic's ethics committee in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions." (Loew 2006, p.63)

Montgomery 1979/82

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, flupenthixol decanoate and placebo drawn from identical matching ampoules Duration: 24 weeks Setting: Outpatient
Participants	Diagnosis: Patients admitted following a suicidal act, having a history of 2 or more previous documented suicidal acts; more than 75% BPD (23 out of 30*; DSM-III, clinical interview)* Age: Flupenthixol group: 38.2 years (SD = 15.53), placebo group: 31.9 (SD = 11.0)* Sex: 21 F, 9 M* Exclusions: Overt schizophrenia or depression, organic illness
Interventions	1. Flupenthixol decanoate intra-muscular: 20 mg every four weeks N = 14 2. Placebo: drawn from identical ampoules N = 16 Concomitant psychotherapy: All patients attended the special crisis intervention clinic within two weeks of the index suicidal act Concomitant pharmacotherapy: Not specified
Outcomes	Suicidal behaviour: Number of participants in each group with/without suicidal act within the 6 months of treatment Adverse effects: Assessed by standard reporting form
Notes	*Only reported for the completers

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Patients were randomly allocated" (Montgomery 1979, p. 227)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Yes	Quote: "intramuscular flupenthixol decanoate or placebo drawn from identical matching ampoules" (Montgomery 1979, p. 227
Blinding? observer-rated outcomes	Yes	Quote: "intramuscular flupenthixol decanoate or placebo drawn from identical matching ampoules" (Montgomery 1979, p. 227)

Montgomery 1979/82 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Quote: "To preserve blindness patients with significant Parkinsonian side effects were removed from the trial and counted as drop outs." (Montgomery 1979, p. 227) Reported dichotomous outcomes based on the completer sample (no further details on drop-out patients concerning diagnosis, sex, and age) Of the 37 patients enrolled, 30 completed treatment (4 drop-outs in the active group leaving 14 completers, 3 drop-outs in the placebo group leaving 16 completers) Reasons for early termination: Parkinsonian side effects: 2 in flupenthixol group/0 in placebo group No reason given: 2/3 Comment: Only dichotomous data used in this review, drop-outs were imputed as having the negative outcome
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Unclear	Comment: Not specified if there was a washout-period or if concomitant psychotropic medication was allowed
Bias due to sponsoring improbable?	Unclear	No details about funding/sponsoring provided.

Montgomery 81/82/83

Methods	Design: RCT Allocation: Randomised Blinding: No further details Duration: 6 months Setting: Outpatient
Participants	Diagnosis: Patients admitted following a suicidal act, having a history of 2 or more previous documented suicidal acts; more than 75% BPD (30 out of 38*; DSM-III, clinical interview) Age: Mianserin group: mean age 35.1 (SD = 12.24), placebo group: mean age 36.2 (SD = 13.38)* Sex: 26 F, 12 M* Exclusions: Overt schizophrenia or depression, organic illness

Montgomery 81/82/83 (*Continued*)

Interventions	1. Mianserin (30 mg nightly) N = 17 completers of N = 29 allocated to mianserin 2. Placebo N = 21 completers of N = 29 allocated to placebo Concomitant psychotherapy: Patients were followed up in a clinic with back up from social workers, community nurses and a crisis intervention team Concomitant pharmacotherapy: Not specified
Outcomes	Suicidal behaviour: Number of participants in each group with/without act of self-harm within the 6 months of treatment Attrition
Notes	*Only reported for the completers

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "randomly allocated" (Montgomery 1981, p. 787)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Unclear	Quote: "double-blind conditions" (Montgomery 1981, p. 787)
Blinding? observer-rated outcomes	Unclear	Quote: "double-blind conditions" (Montgomery 1981, p. 787)
Incomplete outcome data addressed? All outcomes	Yes	Dichotomous outcomes used here are based on the ITT sample, dropped-out patients were imputed as having the negative outcome. Comment: High drop-out rate (20 out of 58; Montgomery 1981, p. 787), but reasons not specified, nor to which treatment group the lost patients belonged. Therefore, drop-outs could not be imputed in categorial outcomes as having the negative outcome
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Unclear	Quote: "Compliance was checked by tablet count." (Montgomery 1983, p. 184S) Comment: Not specified if there was a washout-period or if concomitant psy-

Montgomery 81/82/83 (*Continued*)

		chotropic medication was allowed
Bias due to sponsoring improbable?	Unclear	No details about funding/sponsoring provided.

Nickel 2004

Methods	Design: RCT Allocation: Randomisation was carried out confidentially by the clinic administration and arranged so that twice as many subjects would be treated with the active drug as with placebo Blinding: Tablets were supplied in numbered boxes Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II) Age: Topiramate: mean age 25.5 years, placebo 26.6 years (no further details) Sex: 31 F Exclusions: Actively suicidal patients, abusing alcohol or drugs, major depression, schizophrenia, bipolar disorder, current use of topiramate or other psychotropic medication, psychotherapy, pregnant or planning to become, somatically ill
Interventions	1. Topiramate: 250 mg/day N = 21* 2. Placebo: Matching N = 10* Concomitant psychotherapy: Not allowed Concomitant pharmacotherapy: Not allowed
Outcomes	Impulsivity: STAXI-anger-out Anger: STAXI-trait anger Attrition Adverse effects: Non-structured questionnaire
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Randomization was carried out confidentially by the clinic administration." (Nickel 2004, p. 1516)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered boxes." (Nickel 2004, p. 1516)

Nickel 2004 (*Continued*)

Blinding? self-rated outcomes	Yes	Quote: "blinded medication" (Nickel 2004, p. 1516), "subjects [...] were blinded regarding [...] assignment" (Nickel 2004, p. 1516)
Blinding? observer-rated outcomes	Yes	Quote: "blinded medication" (Nickel 2004, p. 1516), "clinicians [...] were blinded regarding [...] assignment" (Nickel 2004, p. 1516)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Two subjects, who failed to appear 2 to 3 times for the weekly evaluations, dropped out of the study, and their data were not further analyzed. Finally, data from 29 women [...] were evaluated." (Nickel 2004, p. 1516). Continuous outcomes based on available case analysis Of the 31 patients enrolled, 29 completed treatment Reasons for early termination: Failed to appear at least 2 times for weekly evalutaion, no further details: 2 in topiramate group/0 in placebo group
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "exclusion [...] current use of topiramate or other psychotropic medication"
Bias due to sponsoring improbable?	Unclear	Quote: "The authors report no financial affiliation or other relationship relevant to the subject matter of this article." (Nickel 2004, p. 1515)

Nickel 2005

Methods	Design: RCT Allocation: Randomisation was carried out confidentially by the clinic administration, tablets were supplied in numbered boxes Blinding: Double-blind (both clinician and subjects were blinded) Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II) Age: Mean age 29.1 years Sex: 44 M

	Exclusions: Actively suicidal, currently fulfilling criteria for an addictive illness, severe major depression, acute psychosis, bipolar disorder, current use of topiramate or other psychotropic medication, current psychotherapy, somatically ill
Interventions	1. Topiramate: 250 mg/day N = 22* 2. Placebo: matching N = 22* Concomitant psychotherapy: Not allowed Concomitant pharmacotherapy: Psychotropic medication not allowed
Outcomes	Impulsivity: STAXI-anger out Anger: STAXI-trait anger Attrition Adverse effects: Weight
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Randomization was carried out confidentially by the clinic administration." (Nickel 2005, p. 496)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered boxes." (Nickel 2005, p. 496)
Blinding? self-rated outcomes	Yes	Quote: "blinded medication" (Nickel 2005, p. 496) "subjects [...] were blinded regarding [...] assignment" (Nickel 2005, p. 496)
Blinding? observer-rated outcomes	Yes	Quote: "blinded medication" (Nickel 2005, p. 496), "clinicians [...] were blinded regarding [...] assignment" (Nickel 2005, p. 496)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Forty-eight subjects were eligible to take part in the study [...] 44 patients were required [...] randomization was carried out confidentially by the clinical administration [...] 1:1 randomisation ratio for topiramate (TG, N = 22) versus placebo treatment (N = 22)" (Nickel 2005, p. 496) Comment: Unclear, why or how the 44 participants were finally chosen out of the 47

		potential participants Quote: "Two subjects from the placebo group failed to appear appear more than twice for the weekly evaluations and dropped out of the study; their data were not further analyzed. Thus, data from 42 men (42 out of 44) were evaluated." (Nickel 2004, p. 1516). Comment: Reasons for early termination not further specified. Continuous outcomes based on available case analysis. For dichotomous data, drop-outs were imputed as having the negative outcome. Of the 44 patients enrolled, 42 completed treatment (22 in the active group, 20 in the placebo group) Reasons for early termination: Failed to appear more than twice for weekly evaluation, no further reasons given: 0 in the active group, 2 in the placebo group
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "reasons for exclusion were [...] the current use of topiramate or other psychotropic medication." (Nickel 2004, p. 495)
Bias due to sponsoring improbable?	Unclear	Quote: "The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions and its design approved by Ethikkommission der ROMED Kliniken KG. All subjects gave written informed consent. The study was conducted independent of any institutional influence and was not funded, and there were no conflicts of interest." (Nickel 2004, p. 496)

Nickel 2006

Methods	Design: RCT Allocation: Randomisation was carried out confidentially by the clinic administration and arranged so that twice as many subjects would be treated with the active drug as with placebo Blinding: Tablets were supplied in numbered boxes, both patients and clinicians were blinded Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II) Age: Aripiprazole group: mean age 22.1 years (SD = 3.4), Placebo group: mean age 21.2 years (SD = 4.6) Sex: 43 F, 9 M Exclusions: Current suicidal ideation, schizophrenia, current use of aripiprazole or another psychotropic medication, current psychotherapy, pregnancy, planned pregnancy or sexual activity without contraception, severe somatic illness
Interventions	1. Aripiprazole: 15 mg/day N = 26* 2. Placebo: matching dose N = 26* Concomitant psychotherapy: Not allowed Concomitant pharmacotherapy: Not allowed
Outcomes	Interpersonal problems: SCL-90-R-INT (t-value transformed) Impulsivity: STAXI-anger out Self-mutilating behaviour: Number of patients with/without self-injury during the 8 week treatment Anger: SCL-90-R-HOS (t-value transformed), STAXI-trait anger Psychotic symptoms: SCL-90-R-PAR, SCL-90-R-PSY (both t-value transformed) Depression: SCL-90-R-DEP (t-value transformed), Ham-D Anxiety: SCL-90-R-ANX (t-value transformed), HARS General psychiatric pathology: SCL-90-R-GSI (t-value transformed) Adverse effects: Serious side effects, suicidal acts
Notes	*As randomised

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "The random assignment was carried out confidentially by the clinic administration." (Nickel 2006, p. 835)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered boxes." (Nickel 2006, p. 835)

Nickel 2006 (*Continued*)

Blinding? self-rated outcomes	Yes	Quote: "subjects received medication in a blinded manner" (Nickel 2006, p. 835), "the subjects [...] were blinded regarding the assignment (Nickel 2006, p. 835)
Blinding? observer-rated outcomes	Yes	Quote: "subjects received medication in a blinded manner" (Nickel 2006, p. 835), "the clinicians [...] were blinded regarding the assignment (Nickel 2006, p. 835)
Incomplete outcome data addressed? All outcomes	Yes	Of the 52 patients enrolled, 47 completed treatment Quote: "Five subjects who missed more than two weekly evaluations dropped out." (Nickel 2006, p. 835) Comment: Reasons for drop-out not further specified. Quote: "according to the intent-to-treat principle performed with the last observation carried forward" (Nickel 2007, p. 1025) Continuous outcomes based on ITT sample (LOCF) Dichotomous outcomes based on ITT sample Reasons for early termination: Failed to appear more than twice for weekly evaluation, no further reasons given: 5 subjects, no further details
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Criteria for exclusion [...] current use of aripiprazole or another psychotropic medication" (p. 8349
Bias due to sponsoring improbable?	Unclear	Quote: "The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical profession, and its design was approved by the clinic's ethics committee. The study was conducted independently of any institutional influence an was not funded." (Nickel 2006, p. 835)

Pascual 2008

Methods	Design: RCT Allocation: Randomised, randomisation was performed by blocks of 4 generated using the SPSS software package (SPSS Inc., Chicago, Ill) Blinding: Double, no further details Duration: 12 weeks, following a 2-week baseline period Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II, DIB-R) Age: Mean 29.2 years Sex: 49 F, 11 M Exclusions: Schizophrenia, alcohol or other substance dependence, current major depressive episode, bipolar disorder, drug-induced psychosis, organic brain syndrome, mental retardation
Interventions	1. Ziprasidone: flexible dose 40 to 200 mg/day, mean dose 84.1 mg/day (SD 54.4, range 40 - 200 mg/day) N = 30* 2. Placebo: No further details N = 30* Concomitant psychotherapy: Patients participated in weekly, 2-hour, non-specific group psychotherapy sessions Concomitant pharmacotherapy: Allowed to continue with benzodiazepine (max. 40 mg/day), antidepressants, mood stabilisers if initiated prior to inclusion; doses could not be modified
Outcomes	BPD severity: CGI-BPD-global Avoidance of abandonment: CGI-BPD-abandonment Interpersonal problems: CGI-BPD-unstable relations Identity disturbance: CGI-BPD-identity Impulsivity: CGI-BPD-impulsivity, BIS Suicidal ideation: CGI-BPD-suicide Affective instability: CGI-BPD-affect instability Feelings of emptiness: CGI-BPD-emptiness Anger: CGI-BPD-anger Psychotic paranoid symptoms: CGI-BPD-paranoid ideation, BPRS Depression: Ham-D-17, BDI Anxiety: HARS General psychiatric pathology: SCL-90-R-GSI Attrition Adverse effects: treatment-emergent adverse events, EKG, laboratory assessment, UKU Side Effect Rating Scale for extrapyramidal side effects
Notes	*As randomised

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Yes	Quote: "Randomization was performed by blocks of 4 generated using the SPSS software package" (p. 604)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Unclear	Quote: "double-blind" (p. 604) Comment: No further information given
Blinding? observer-rated outcomes	Unclear	Quote: "double-blind" (p. 604) Comment: No further information given
Incomplete outcome data addressed? All outcomes	No	Quote: "All analyses were conducted on an intent-to-treat basis. [...] Patients were included in the analyses only if they had a baseline measure and at least 1 postbaseline measure. [...] The end point was based on a last-observation-carried-forward (LOCF) strategy." (p. 604 et seq.) Comment: intent-to-treat data refer to all participants that were randomly assigned and initiated the experimental phase (p. 605) However, it remains unclear for which reason 5 out of the 65 eligible subjects "dropped out during the selection phase" (p. 605) Reasons for drop-out specified and balanced across the two groups, including withdrawal due to "clinician decision/insufficient treatment effect (p. 605 et seq.) Continuous data based on LOCF data of the ITT sample Dichotomous data based on ITT sample Of the 60 patients enrolled, 29 completed the full 12 weeks of the trial (13 in ziprasidone group, 16 in placebo group) Reasons for early termination: Need of psychiatric hospitalization: 4 in ziprasidone group/3 in placebo group, Adverse events/patient decision: 9/4, Clinician decision/insufficient treatment effect 3/7, Other reasons: 1/0
Free of selective reporting?	Yes	Comment: The study protocol is available and all of the study's pre-specified primary and secondary outcomes that are of interest in the review are reported in the pre-specified way.

Pascual 2008 (*Continued*)

Free of other bias?	Unclear	Quote: "Compliance was assessed by direct questioning of patients and by counting the capsules returned at follow-up visits." Quote: "patients were allowed to continue with benzodiazepines [max. 40 mg/day], antidepressants, and mood stabilisers if they had been initiated prior to inclusion, but doses could not be modified during the study." (p. 604)
Bias due to sponsoring improbable?	No	Quote: "This study was supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain), the REM-TAP Network, and Pfizer, Madrid, Spain. The authors report no additional financial or other relationships relevant to the subject of this article." (p. 603)

Reich 2009

Methods	Design: RCT Allocation: Randomised (prearranged random number sequence) Blinding: Double Duration: 12 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, DIB-R $\geqq$ 8) Age: Mean 31.2 years Sex: 24 F, 3 M Exclusions: Diagnosis of dementia, psychiatric disorder secondary to a general medical condition, bipolar disorder, or psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features); diagnosis of substance dependence (active within last 60 days); currently being hospitalized; unstable general medical condition; previous treatment with lamotrigine for 1 week or more; enrollment in a drug study within last 60 days; enrollment in psychotherapy in the last 30 days; active suicidal or homicidal ideation; pregnancy or nursing
Interventions	1. Lamotrigine: flexible dose 25 to 275 mg/day, mean final dose 106.7 mg (range 25 - 225 mg/day) N = 15* 2. Placebo: No further details N = 12 (one patient of the 13 assigned to placebo was disqualified because of failure to adhere to the study protocol and not included in analyses) Concomitant psychotherapy: Patients enrolled in psychotherapy in the last 30 days were not eligible Concomitant pharmacotherapy: Patients could be taking one antidepressant, but had to have been on a stable dose of this medication for 1 month.

Outcomes	BPD severity: ZAN-BPD total score Impulsivity: ZAN-BPD-impulsivity score Affective instability: ZAN-BPD-affective instability score, ALS Attrition Adverse effects: rash
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "patients were randomized [...] in a 1:1 manner. This was determined by a pre-arranged random number sequence." (p. e-3). Twenty-eight patients completed all aspects of assessment before randomization. Fifteen patients were randomized to receive lamotrigine, and 13 patients were assigned to receive placebo." (p. e-3)
Allocation concealment?	Unclear	Insufficient information to permit judgement of 'Yes' or 'No' (unclear, if the number sequence was kept confidentially or if enrolling investigators could possibly foresee assignment)
Blinding? self-rated outcomes	Yes	No self-rated outcomes used for this review
Blinding? observer-rated outcomes	Yes	Quote: "double-blind placebo-controlled study" (e.g. p. e-1); "double-distinction between "prescribing psychiatrist (D.B.R.)" who fixed the dose and "study staff" who made assessments (p. 3)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "One patient in the placebo group was disqualified because of failure to adhere to the study protocol." (p. e-3) Not clear if the reported mean changes are based on the ITT sample or completers only.
Free of selective reporting?	Yes	Comment: The study protocol is available and all of the study's pre-specified primary and secondary outcomes that are of interest in the review are reported in the pre-specified way.

Free of other bias?	Unclear	Quote: "Patients could be taking one antidepressant, but had to have been on a stable dose of this medication for 1 month." (p. e-2)
Bias due to sponsoring improbable?	No	Quote: "The study was supported by a grant from GlaxoSmithKline." (p. e-5)

Rinne 2002

Methods	Design: RCT, followed by single-blind half crossover and an open treatment phase; only the first RCT phase will be regarded in the following Allocation: Randomised, no further details Blinding: Double-blind, no further details Duration: 6 weeks, patients had to be medication free for at least 2 weeks before entering the trial Setting: Outpatients
Participants	Diagnosis: BPD (DSM-IV, SCID-II) + score of 110 or more on the borderline trait and distress scale of a self-report screener for personality disorders (ADP-IV) + score of 20 or more on the BPDSI Age: 29.2 (SD = 7.6) Sex: 38 F Exclusions: n.s.
Interventions	1. Fluvoxamine: 150 mg/day N = 20* 2. Placebo: No further details N = 18* Concomitant psychotherapy: Two patients who began psychotherapy dropped-out the study; thus, psychotherapeutic treatment is likely to not have been allowed Concomitant pharmacotherapy: Patients had to stop taking all psychoactive drugs and be medication free for at least 2 weeks before entering the trial (6 weeks for fluoxetine)
Outcomes	Impulsivity: BPDSI-impulsivity Affective instability: BPDSI-rapid mood shifts Anger: BPDSI-anger Attrition Adverse effects: Any, number of subjects experiencing specific adverse events (not used here as data refer to intermediate assessment, whereas post-treatment data are not available)
Notes	*As randomised

Risk of bias

Item	**Authors' judgement**	**Description**

Rinne 2002 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "randomized trial" (p. 2049)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Unclear	Quote: "double-blind" (p. 2049) Comment: No further information given
Blinding? observer-rated outcomes	Unclear	Quote: "double-blind" (p. 2049) Comment: No further information given
Incomplete outcome data addressed? All outcomes	Yes	Quote: "The final study group comprised the 38 subjects eligible for participation" (p. 2049), "an intent-to-treat analysis was performed" (p. 2050) Continuous outcomes based on ITT, BMDP imputation technique used for drop-outs Of the 38 patients enrolled, 35 completed the RCT phase (19 in active drug group, 16 in placebo group) Reasons for early termination: Serious aggravation of self-damaging behaviours: 0 in the fluvoxamine group, 2 in the placebo group Severe side effects: 1/0
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "The participants had to stop taking all psychoactive drugs [...] and they all had to be medication free for at least 2 weeks before entering the trial; the medication -free interval was 6 weeks for fluoxetine." (p. 2049)
Bias due to sponsoring improbable?	No	Quote: "Supported by the De Geestgronden Institute of Mental Health Care, by Stichting tot Steun of Vereiniging Bennekom, by national Fund for Menal Health grant 4820, and by Solvay Pharma." (p. 2053)

Salzman 1995

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, active drug and placebo administered in identical capsules Duration: 12 weeks (after 1 week placebo run-in) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-III-R; DIB-R, SCID-II, clinical interview) Age: Mean age of fluoxetine group: 37.0 (no further details), placebo group: 35.6 (no further details)* Sex: 14 F, 8 M* Exclusions: Self-mutilating behaviours during the past 4 years, recent suicidal behaviour, current suicidal or aggressive behaviour, current substance abuse or excessive daily alcohol use (> 2 drinks/day), history of psychiatric hospitalization, concurrent secondary axis II disorder, major depression or other axis I disorder
Interventions	1. Fluoxetine: maximum of 60 mg/day, according to needs of the patient and in accordance with package insert guidelines; mean daily dose 40 mg/day Completers: N =13 2. Placebo: No further details Completers: N = 9 Data are only reported for treatment completers Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Not allowed
Outcomes	Anger: PDRS-anger, POMS-anger, OAS-M-anger against objects Depression: Ham-D, PDRS-depression, POMS-depression Mental health status: GAS
Notes	* Completers only

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "random-assignment comparison" (p. 24)
Allocation concealment?	Unclear	Comment: No information given
Blinding? self-rated outcomes	Yes	Comment: No self-rated outcomes used within this review
Blinding? observer-rated outcomes	Yes	Quote: "Subjects were evaluated by independent observers" (p. 24)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Thirty-one subjects met criteria for this study; four decided not to enroll and were lost to follow-up. Of 27 subjects who enrolled in the study, 22 completed

Salzman 1995 (*Continued*)

		the trial. One subject dropped out because she wanted assurance that she would be in the medication group; four others dropped out without explanation and were lost to follow-up." (p. 24) Of the 27 patients enrolled, 22 completed treatment Reasons for early termination: Wanted assurance to be in the active drug group: 1 (not specified, which group) Dropped out without explanation: 4 (not specified, which group) Comment: Continuous outcomes based on completer analysis
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Subjects were not included [...] if they were taking any other psychotropic medication"; "1-week placebo run-in" (p. 24),
Bias due to sponsoring improbable?	Unclear	No details provided.

Schulz 2007

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind; olanzapine started at 2.5 or 5.0 mg/d at investigator's discretion, flexible dose thereafter Duration:12 weeks (after screening period of 2 - 14 days) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV; DIPD-IV) + ZAN-BPD total score of 9 or higher Age: Olanzapine group mean age 31.79 (SD = 9.54), placebo group mean age 31.83 (SD = 9.62) Sex: 223 F, 91 M Exclusions: Bipolar disorder, schizophrenia, major depressive disorder or substance dependence within last 3 months, current PTSD, panic disorder, or obsessive-compulsive disorder
Interventions	1. Olanzapine: flexible dose, 2.5 to 20 mg/day, mean modal dose 7.09 mg/day N = 150 2. Placebo: No further details N = 155 Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: No medications with primarily CNS activity (except for protocol-specified benzodiazepines and hypnotics)

Outcomes	BPD severity: number of patients in each group with response/no response, i.e. 50% reduction at least in ZAN-BPD total score Avoidance of abandonment: ZAN-BPD-frantic efforts to avoid abandonment Interpersonal problems: ZAN-BPD unstable interpersonal relationships Identity disturbance: ZAN-BPD-identity disturbance Impulsivity: ZAN-BPD-impulsivity, OAS-M-aggression Suicidal ideation: OAS-M-suicidal ideation Suicidal behaviour: ZAN-BPD-suicidal or self-mutilating behaviour Affective instability: ZAN-BPD-affective instability Feelings of emptiness: ZAN-BPD-chronic feelings of emptiness Anger: ZAN-BPD-intense anger, OAS-M-irritability, SCL-90-R-HOS Dissociative symptoms: ZAN-BPD-paranoid ideation of disassociation Depression: MADRS General psychiatric pathology: SCL-90-R GSI Mental health status: Sheehan Disability Scale-total, GAF Attrition Adverse effects: weight, Simpson-Angus Scale, BARS, AIMS
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "patients [...] were randomly assigned to treatment" (Eli Lilly, 2008, p. 15) , "All participants, study site personnel and investigators were masked to randomisation codes." (Schulz 2008, p. e1) Comment: Randomisation conducted centrally
Allocation concealment?	Yes	Quote: "All participants, study site personnel and investigators were masked to randomisation codes." (Schulz 2008, p. e1)
Blinding? self-rated outcomes	Yes	Quote: "All participants, study site personnel and investigators were masked to randomisation codes." (Schulz 2008, p. e1)
Blinding? observer-rated outcomes	Yes	Quote: "All participants, study site personnel and investigators were masked to randomisation codes." (Schulz 2008, p. e1)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Analyses were done on an intent-to-treat basis [...] In general, LOCF mean change analyses" (Eli Lilly, 2008, p. 5)

		Quote: "Of the 314 randomized patients, 305 had both a baseline and a non-missing post-baseline observation and were thus qualified for the primary efficacy analysis." (Eli Lilly, p. 16) Comment: Unclear, what "non-missing post-baseline observation" exactly means. However, discontinuing participants were enclosed in the 305 participants whose results were analysed using LOCF. Continuous outcomes based on LOCF / ITT 314 patients were enrolled and randomly allocated. Outcomes refer partly to all of them, partly to 310 or 305 patients. No further details given.
Free of selective reporting?	No	Comment: Several outcome measures (secondary and adverse events) are reported that were not pre-specified according to the study protocol.
Free of other bias?	Unclear	Quote: "No medication with primarily CNS acitivity (except for protocol-specified benzodiazepines and hypnotics)" (p.EliLilly, p. 4)
Bias due to sponsoring improbable?	No	Quote: "This study was sponsored by Eli Lilly. S.C.S. has received honorarium from Eli Lilly, AstraZeneca and Bristol-Meyers Squibb; grant fees from Eli Lilly, AstraZeneca, Abbott, MIND Institute and the NIMH; and consultation fees from Eli Lilly, AstraZeneca and Vanda. H.C.D., Q.T., Y.T., D.L. and S.C. are employed by Lilly Research Laboratories." (p. e-1)

Simpson 2004

Methods	Design: RCT Allocation: Randomised block assignment, equal number of patients with major depressive disorder, PTSD, or both were assigned to each treatment condition in order to minimize the possible confound to treatment response Blinding: Double-blind, a non-treating study psychiatrist was available to break the blind in the event of a clinical emergency, but didn't occur Duration: 12 weeks (after a 1-week placebo run-in) Setting: Partial hospitalization
Participants	Diagnosis: BPD (DSM-IV, SCID-II), patients had to meet at least one BPD criterion pertaining to affective instability or anger and one pertaining to impulsivity Age: Fluoxetine completers mean age 39.78 (SD = 9.81), placebo completers mean age 32.73 (SD = 10.76) Sex: 25 F Exclusions: Primary diagnosis of substance dependence, seizure disorder, unstable medical conditions, lifetime history of schizophrenia or bipolar disorder, MAOI treatment in the prior 2 weeks, previous adequate trial of fluoxetine, pregnancy, lactating women, unwillingness to use effective contraception
Interventions	1. DBT (weekly 1-hour sessions of individual DBT, weekly 2-hour skills group, round-the-clock emergency consultation availability) + fluoxetine 40 mg/day N = 12 2. DBT (weekly 1-hour sessions of individual DBT, weekly 2-hour skills group, round-the-clock emergency consultation availability) + placebo (no further details) N = 13 Data are only available for the 20 completers (fluoxetine N = 9, placebo N = 11) Concomitant psychotherapy: Patients were recruited from a partial hospital program, all received DBT as depicted above Concomitant pharmacotherapy: Only other psychotropic allowed was 50 to 100 mg/day trazodone for insomnia
Outcomes	Impulsivity: OAS-M-aggression, STAXI-anger out Suicidal ideation: OAS-M-suicidality Self-mutilating behaviour: OAS-M-assault against self Psychotic symptoms/dissociation: DES Depression: BDI Anxiety: STAI-trait Mental health status: GAF Attrition: number of patients lost after randomisation
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomized block assignment minimized the possible confound of co-morbid axis-I presentations expected to re-

		sponse to fluoxetine by assignment of an equal number of patients with major depressive disorder, posttraumatic stress disorder, or both to each treatment condition." (p. 380)
Allocation concealment?	Unclear	Comment: No information given.
Blinding? self-rated outcomes	Unclear	Quote: "This study was double-blind" (p. 380) Comment: No information given how blinding of participants was attempted, especially in light of the day-clinic setting with possibly shared group therapy.
Blinding? observer-rated outcomes	Yes	Quote: "This study was double-blind" (p. 380), "A non-treating study psychiatrist was available to break the blind in event of a clinical emergency." (p. 381) Comment: In contrast, the treating clinician was probably blind.
Incomplete outcome data addressed? All outcomes	No	Of the 25 patients enrolled, 12 were randomised to fluoxetine and 13 to placebo. 20 completed treatment (9 in fluoxetine group, 11 in placebo group) Reasons for early termination: Negative experience of the placebo washout period, which led to a reversal of their willingness to tolerate a potential assignment to the placebo condition: 3 in fluoxetine group, 0 in placebo group Sought hospitalization at another facility: 0/1 Intolerable lack of improvement: 0/1 Comment: Reasons for early termination specified (p. 381) Continuous outcomes are only reported for study completers, while drop-outs could be imputed as having the negative outcome for dichotomous data.
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Diary card records of pill ingestion were reviewed, and pill counts were made as a compliance measure." (p. 381) Quote: "1-week placebo run-in" (p. 380),

Simpson 2004 (*Continued*)

		"the only other medication allowed was 50 to 100 mg/day of trazodone for insomnia." (p. 381)
Bias due to sponsoring improbable?	No	Quote:"Support for this study was provided by the Department of Psychiatry and Human Behaviour at Brown Medical School and Eli Lilly."

Soler 2005

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, no further details Duration: 12 weeks (after a 4 weeks selection phase during which the pre-intervention baseline was established but no therapeutic intervention was given) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II and DIB-R), CGI-S score of at least 4 Age: DBT + olanzapine group mean age: 27.57 (SD = 6.3), DBT + placebo group mean age: 26.33 (SD = 5.4) Sex: 52 F, 8 M) Exclusions: Comorbid unstable axis I disorder, women not using medically accepted contraception
Interventions	1. DBT + olanzapine: weekly 150-minute skills training group sessions, phone calls + olanzapine flexible dose between 5 to 20 mg/day (mean dose 8.83 mg/day, SD = 3.8) N = 30* 2. DBT + placebo: weekly 150-minute skills training group sessions, phone calls + placebo (no further details) N = 30* Concomitant psychotherapy: All patients received DBT as depicted above Concomitant pharmacotherapy: Subjects could continue treatment with benzodiazepines, antidepressants, and mood stabilisers, but doses could not be modified
Outcomes	Impulsivity: Behavioural biweekly reports of episodes of impulsivity/aggressive behaviour Suicidal behaviour/self-mutilating behaviour: behavioural biweekly reports of episodes of self-injuring behaviour/suicide attempts Depression: Ham-D Anxiety: HARS Mental health status: CGI-S Attrition Adverse effects: As reported by patients, scales assessing extrapyramidal side effects, weight, cholesterol levels
Notes	

Soler 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "randomly assigned to receive dialectical behaviour therapy plus either olanzapine or placebo on a 1:1 ratio" (p. 1222)
Allocation concealment?	Unclear	Comment: No information given.
Blinding? self-rated outcomes	Unclear	Quote: "double blind [...] study
Blinding? observer-rated outcomes	Unclear	Quote: "double blind [...] study
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "All analyses were conducted on an intent-to-treat basis. The endpoint was based on a last-observation-carried-forward strategy. Patients were included in the analyses only if they had a baseline measure and at least one post-baseline measure." (p. 1222) "Quote: Sixty subjects were randomly assigned to dialectical behaviour therapy plus olanzapine or placebo and started the experimental phase; 42 subjects (70%) completed the study.There were no between-group differences regarding demographic variables or concomitant treatments at baseline. Neither dialectical behaviour therapy intervention time nor dropout rates differed significantly between the two groups (eight of the 30 patients who received olanzapine versus 10 of the 30 who received placebo dropped out before the end of the study." (p. 1222 et seq.) Comment: reasons for drop-out given; numbers balanced across groups Continuous outcomes based on ITT (LOCF) Of the 60 patients enrolled, 42 completed treatment (22 in active drug group, 20 in placebo group) Reasons for early termination: No reasons given

Free of selective reporting?	Yes	Comment: The study protocol is available and all of the study's pre-specified primary and secondary outcomes that are of interest in the review are reported in the pre-specified way.
Free of other bias?	Unclear	Quote: "Patients could continue treatment with benzodiazepines, antidepressants, and mood stabilisers, but doses could not be modified." (p. 1222)
Bias due to sponsoring improbable?	No	Quote: "Supported by grants from the Fondo de Investigación Sanitaria (Ministry of Health, Spain) and from Eli Lilly and Co. Madrid." (p. 1223)

Soloff 1989

Methods	Design: RCT Allocation: Randomised Blinding: Double-blind, no further details Duration: 5 weeks (after 1-week washout) Setting: Inpatient (after 3 weeks some allowed to complete as outpatients)
Participants	Diagnosis: BPD (DSM-III, DIB), GAS score of 50 or less and either score of 17 or higher on the Ham-D or 66 or greater on the IMPS Age: Mean 25.1 years, no further details Sex: 68 F, 22 M Exclusions: Schizophrenia, mania, related disorders, chronicity of illness, organicity
Interventions	1. Amitriptyline: Mean dose after 3 weeks of treatment: 149.1 mg/day, plasma levels of 240.4 ng/mL amitriptyline + nortriptyline (SD = 99.4) N = 29 2. Haloperidol: Mean dose after 3 weeks of treatment 4.8 mg/day, plasma level of 8.66 ng /mL (SD = 3.7) N = 28 3. Placebo: No further details N = 28 Concomitant psychotherapy: Patients were treated as psychiatric inpatients for at least 3 weeks, no further details Concomitant pharmacotherapy: Biperiden hydrochloride (2 mg) was allowed as needed for extrapyramidal reactions
Outcomes	Interpersonal problems: SCL-90-INT Impulsivity: Ward Scale of Impulsive Action Patterns, BIS, STIC Anger: SCL-90-HOS, BDHI, BDHI Psychotic symptoms: SCL-90-PAR, SCL-90-PSY, IMPS, SSI Depression: SCL-90-DEP, Ham-D, BDI

	Anxiety: SCL-90-ANX General psychiatric pathology: SCL-90-GSI Mental health status: GAS Attrition Adverse effects
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Patients were randomly assigned" (Soloff 1986, p. 692)
Allocation concealment?	Yes	Quote: "Numbered tablets [...] were given" (Soloff 1986, p. 692)
Blinding? self-rated outcomes	Unclear	Quote: "Double-blind [...] trial" (Soloff 1989, p. 239)
Blinding? observer-rated outcomes	Yes	Quote: "Weekly ratings by two 'blind investigators', an onward psychiatrist serving as the nonblind psychiatrist (for safety)." (Soloff 1986, p. 693)
Incomplete outcome data addressed? All outcomes	Yes	Quote: "Five patients failed to complete the minimum two weeks on medication needed for inclusion in outcome analysis, one taking amitriptyline, three taking haloperidol, and one taking placebo." (Soloff 1989, p. 242) Continuous outcomes based on LOCF / ITT A minimum of 2 weeks receiving medication was required to include data for endpoint analysis Of the 90 patients enrolled, 85 completed treatment (29 in amitriptyline group, 28 in haloperidol group, 28 in placebo group) Reasons for early termination: Failed to complete the minimum 2 weeks on medication needed for inclusion in outcome analysis (1 in amitriptyline group, 3 in haloperidol group, 1 in placebo group) Comment: Reasons for drop-out not further specified. Total number of drop-outs small, though, and balanced across groups

Soloff 1989 (*Continued*)

Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Patients were kept free of all medication for 7 days" (Soloff 1989, p. 239) , "Biperiden hydrochloride (2 mg) was allowed as needed for extrapyramidal reactions" (Soloff 1986, p. 692)
Bias due to sponsoring improbable?	Yes	Quote: "This work was supported by NIMH grants 35392, MHCRC 30915, and MH00658." (p. 245)

Soloff 1993

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, no further details Duration: 5 weeks (after 1-week washout) Setting: Patient in the hospital for a minimum of 2 weeks and after discharge were seen weekly as outpatients
Participants	Diagnosis: BPD (DSM-III-R, DIB), GAS score of 50 or less and either score of 17 or higher on the Ham-D or 66 or greater on the IMPS Age: Mean 26.7 years (SD=7.2) Sex: 82 F, 26 M Exclusions: Drug- and/or alcohol-related deficits or physical dependence, evidence of central nervous system disease, physical disorders of known psychiatric consequence, borderline mental retardation
Interventions	1. Haloperidol up to 6 mg/day (six tablets); average dose after 3 weeks of medication 3.93 mg/day (SD = 0.65); mean plasma level by 4 weeks 5.29 ng/mL (SD = 4.04) N = 30 2. Phenelzine sulfate up to 90 mg/day (six tablets); average dose after 3 weeks of medication 60.45 mg/day (SD = 9.55); mean plasma level by 3 weeks 77.54% platelet MAO inhibition (SD = 16.97) N = 34 3. Placebo up to six tablets; average dose after 3 weeks of medication 4.31 tablets/day (SD = 0.6) N = 28 Concomitant psychotherapy: Not specified, patients were inpatients, some were allowed after 2 weeks to complete as outpatients Concomitant pharmacotherapy: Patients were at the start kept free of medication for at least 7 days in order to washout street drugs or prescribed medications
Outcomes	BPD severity: Borderline Syndrome Index Interpersonal problems: ADDS - rejection sensitivity Impulsivity: Ward Scale of Impulsive Action Patterns, BIS, STIC

Soloff 1993 (*Continued*)

	Anger: SCL-90-HOS, BDHI, BDHI, ADDS-reactivity Psychotic symptoms: SCL-90-PAR, SCL-90-PSY, IMPS, SSI Depression: SCL-90-DEP, Ham-D, BDI Anxiety: SCL-90-ANX General psychiatric pathology: SCL-90-GSI Mental health status: GAS Attrition Adverse effects: Weight gain
Notes	*Completers only

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Patients were randomly assigned." (p. 378)
Allocation concealment?	Unclear	Quote: "double-blind [...] trial" (p. 377)
Blinding? self-rated outcomes	Yes	Average daily doses of medication, including placebo pseudo-dose, are given (p. 380) Comment: The measures undertaken to ensure blinding seem elaborated and are described in detail, so the blinding of participants seems to have been thoroughly ensured.
Blinding? observer-rated outcomes	Yes	Quote: "Medication could be increased up to six tablets (haloperidol, 6 mg; phenelzine sulfate, 90 mg; placebo, six tablets)" (p. 378) Average daily doses of medication, including placebo pseudo-dose, are given (p. 380) Comment: The measures undertaken to ensure blinding seem elaborated and are described in detail, so the blinding of the rating study personnel seems to have been thoroughly ensured.
Incomplete outcome data addressed? All outcomes	Yes	Quote: "Sixteen patients failed to complete the minimum 3 weeks of medication required for end-point analysis (p. 380) Comment: Reasons for these drop-outs not further specified. Total number of drop-outs small, though, and balanced across groups Continuous outcomes based on all cases with a minimum of 3 weeks of medication

Soloff 1993 (*Continued*)

		exposure Of the 108 patients enrolled, 92 completed treatment (30 in haloperidol group, 34 in phenelzine group, 28 in placebo group) Reasons for early termination: Relating to medication assignment (e.g. side effects), clinical worsening, factors unrelated to the protocol; not specified by group Patients failing to complete the minimum 3 weeks of medication required for end-point analysis: 6 in the haloperidol group, 4 in the phenelzine group, 6 in the placebo group
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Patients were at the start kept free of medication for at least 7 days to [...] washout street drugs or prescribed medications." (p. 378)
Bias due to sponsoring improbable?	Yes	Quote: "This study was supported by National Institute of Mental Health grant MH35392 and by Clinical Research Center grant MH30915." (p. 697)

Tritt 2005

Methods	Design: RCT Allocation: Randomization in secrecy by the clinic administration so that twice as many subjects would be treated with the active drug compared to placebo Blinding: Double-blind, tablets were supplied in numbered bottles Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, SCID-II) Age: Lamotrigine group mean age 29.4, no further details; placebo group mean age 28.9, no further details Sex: 27 F Exclusions: Actively suicidal, abusing alcohol or drugs, major depression, bipolar disorder, schizophrenia, current use of lamotrigine or other psychotropic medication, psychotherapy, pregnant or planning to be or not using contraception, somatically ill
Interventions	1. Lamotrigine: final dose 200 mg/day (one blinded capsule medication daily) N = 18 2. Placebo, one blinded capsule medication daily N = 9

	Concomitant psychotherapy: Other psychotropic medication not allowed Concomitant pharmacotherapy: Not allowed
Outcomes	Impulsivity: STAXI-anger out Anger: STAXI-trait Attrition Adverse effects: Non-structured questionnaire, patients were asked to note down any new symptoms, weight
Notes	Continuous outcomes based on ITT data (LOCF)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Randomization was carried out confidentially in secrecy by the clinic administration section" (Tritt 2005, p. 288)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered boxes." (Tritt 2005, p. 288)
Blinding? self-rated outcomes	Yes	Quote: "Each individual received one blinded capsule medication daily [...] Both subjects and clinicians were blinded regarding assignment." (Tritt 2005, p. 288)
Blinding? observer-rated outcomes	Yes	Quote: "Each individual received one blinded capsule medication daily [...] Both subjects and clinicians were blinded regarding assignment." (Tritt 2005, p. 288)
Incomplete outcome data addressed? All outcomes	No	Quote: "Thirty-eight subjects were eligible to take part in the study [...] The necessary sample size was calculated [...] This resulted in a group size of n = 27 patients [...] active drug (n=18) compared to placebo (n = 9)" (Tritt 2005, p. 288) Comment: Not clear, why or how the 27 participants were finally chosen out of the 38 potential participants
Free of selective reporting?	No	Comment: All outcomes (i.e. one assessment instrument) reported as planned to be assessed are also reported. However, it seems implausible to use only one assessment instrument in such a complex trial. There is no protocol available to check the

Tritt 2005 (*Continued*)

		pre-defined outcome measure(s).
Free of other bias?	Yes	Quote: "reasons for exclusion were [...] current use of lamotrigine or other psychotropic medication " (p. 288).
Bias due to sponsoring improbable?	Yes	Quote: "The study was conducted independently of any institutional influence and was not funded." (p. 288)

Zanarini 2001

Methods	Design: RCT Allocation: Numbered bottles containing drug or placebo as determined by a random number sequence Blinding: Tablets were supplied in numbered bottles containing drug or placebo Duration: 6 months Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV; DIB-R) Age: Olanzapine group mean age 27.6 years (SD = 7.7), placebo group mean age 25.8 years (SD = 4.5) Sex: 28 F Exclusions: Actively abusing alcohol or drugs, acutely suicidal, current or lifetime schizophrenia, schizoaffective disorder, bipolar disorder, medically ill, seizure disorder, pregnant or planning to be, breastfeeding, not using reliable forms of contraception, having been treated with olanzapine, being prescribed any psychotropic medication that patients thought was helpful
Interventions	1. Olanzapine 2.5 mg/day at beginning, adjusted according to perceived response and side effects, mean dose at endpoint 5.33 mg/day (SD = 3.43); endpoint mean number of tablets/day 1.1 (SD = 0.68) N = 19 2. Placebo: Endpoint mean number of tablets/day 1.2 (SD = 0.75) N = 9 Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: No other psychotropic medication allowed
Outcomes	BPD severity Avoidance of abandonment Interpersonal problems: SCL-90-INT Identity disturbance Impulsivity Suicidal ideation Suicidal behaviour Self-mutilating behaviour Affective instability Feelings of emptiness

	Anger: SCL-90-HOS Psychotic symptoms: SCL-90-PAR, SCL-90-PSY, PANSS Dissociative symptoms: DES Depression: SCL-90-DEP, Ham-D, Anxiety: SCL-90-ANX General psychiatric pathology: SCL-90-GSI Mental health status: GAF Attrition Adverse effects: Weight, Simpson-Angus Scale, BARS, AIMS, structured questionnaire
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "random number sequence" (p. 850)
Allocation concealment?	Yes	Quote: "Tablets were supplied in numbered bottles containing drug or placebo as determined by a random number sequence." (p. 850)
Blinding? self-rated outcomes	Yes	Quote: "Each tablet contained either 2.5 mg of olanzapine or matching inert placebo. [...] Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken after the acquisition of all endpoint data for all subjects." (p. 850)
Blinding? observer-rated outcomes	Yes	Quote: "Each tablet contained either 2.5 mg of olanzapine or matching inert placebo. [...] Both subjects and clinicians were blinded to olanzapine/placebo assignment. The blind was broken after the acquisition of all endpoint data for all subjects." (p. 850)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "Thirty subjects completed all aspects of pre-randomization assessment. However, 2 of these subjects were excluded [...] because it was determined that they were responding well to a selective serotonin reuptake inhibitor. Twenty-eight subjects entered the trial and were randomly assigned [...] All [...] completed at least 2 post-baseline visits and were in-

Zanarini 2001 (*Continued*)

		cluded in all subsequent analyses." (p. 851) Of the 28 patients enrolled, 9 completed treatment (8 in olanzapine group, 1 in placebo group) Reasons for early termination: Sedation: 1 in olanzapine group, 0 in placebo group Increased anxiety or depression: 3/2 Perceived weight gain: 2/0 Lost to follow-up: 5/6 Continuous outcomes based on ITT sample (LOCF) Comment: Overall high drop-out rate but adequately addressed.
Free of selective reporting?	No	Quote: "Due to the small number of subjects, results pertaining to secondary outcome measures will not be reported." (p. 851)
Free of other bias?	Yes	Quote: "excluded if [...] currently were being prescribed any psychotropic medication that they thought was helping" (p. 850)
Bias due to sponsoring improbable?	No	Quote: "Supported, in part, by a grant from Eli Lilly." (p. 849)

Zanarini 2003

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV; DIB-R) Age: Mean age 26.3 years (SD = 6.2) Sex: 30 F Exclusions: Major depressive episode, current or lifetime schizophrenia, schizoaffective disorder, bipolar I or bipolar II disorder
Interventions	1. Ethyl-eicosapentaenoic acid (E-EPA): 1 g/day N = 20 2. Placebo: Mineral oil N = 10 Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Not specified

Zanarini 2003 (*Continued*)

Outcomes	Impulsivity: MOAS Depression: MADRS Attrition Adverse effects: Structured questionnaire
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomly assigned [...] 2:1 randomization ratio." (p. 168)
Allocation concealment?	Unclear	Comment: No information given.
Blinding? self-rated outcomes	Unclear	Quote: "double- blind study" (p. 167), "subjects received two capsules per day [...] each contained either [...] E-EPA or placebo" (p. 167)
Blinding? observer-rated outcomes	Unclear	Quote: "double- blind study" (p. 167), "subjects received two capsules per day [...] each contained either [...] E-EPA or placebo" (p. 167)
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "The three subjects who discontinued their participation (two taking E-EPA and one taking placebo) did so because of life events unrelated to the study." (p. 168) of the 30 patients enrolled, 27 completed treatment (18 in E-EPA group, 9 in placebo group) reasons for early termination: life events unrelated to the study: 2 in E-EPA group, 1 in placebo group Comment: Continuous outcomes are based on completers only.
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Potential subjects were excluded if they were [...] currently being prescribed any psychotropic medication" (p. 167)

Zanarini 2003 (*Continued*)

Bias due to sponsoring improbable?	No	Quote: "Capsules were supplied by Laxdale Pharmaceuticals (Stirling, U.K.)" (p. 167) , "Supported by an Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression to Dr. Zanarini." (p. 169)

Zanarini 2004

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, dose was adjusted by an unblinded psychiatrist according to perceived response and side effects Duration: 8 weeks Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV, DIB-R) Age: Mean age 23 years (SD = 5.7) Sex: 45 F Exclusions: Current major depression, current or lifetime schizophrenia, schizoaffective disorder, bipolar disorder
Interventions	1. Fluoxetine: Mean dose at endpoint 15.0 mg/day (SD = 6.5, range 10.0 - 30.0 mg/day) N = 14 2. Olanzapine: Mean dose at endpoint 3.3 mg/day (SD = 1.8, range 2.5 - 7.5 mg/day) N = 16 3. Fluoxetine + olanzapine: Mean dose at endpoint 12.7 mg/day fluoxetine (SD = 5.9, range 10.0 - 30.0 mg/day) and 3.2 mg/day olanzapine (SD = 1.5, range 2.5 - 7.5 mg/day) N = 15 Concomitant psychotherapy: Not specified Concomitant pharmacotherapy: Not specified
Outcomes	Impulsivity: OAS-M total Depression: MADRS Attrition Adverse effects: Weight, Simpson-Angus Rating Scale, BARS, AIMS, structured questionnaire
Notes	

Risk of bias

Item	Authors' judgement	Description

Zanarini 2004 (*Continued*)

Adequate sequence generation?	Unclear	Quote: "The randomization procedure was designed to assign equal numbers of subjects to the 3 treatment groups." (p. 904)
Allocation concealment?	No	Quote: "Forty-five subjects entered the trial and were randomized to fluoxetine (N = 14), olanzapine (N = 16), or OFC (N = 15) ." (p. 905) Comment: Allocation probably not adequately concealed, since equal numbers were intended (cf. to item above), but group sizes differed, actually.
Blinding? self-rated outcomes	Yes	Quote: "Dose was adjusted by an unblinded psychiatrist according to perceived response and side effects. Both subjects and raters were blinded to study assignment. The blind was broken after acquisition of all endpoint data for all subjects." (p. 904)
Blinding? observer-rated outcomes	Yes	Quote: "Dose was adjusted by an unblinded psychiatrist according to perceived response and side effects. Both subjects and raters were blinded to study assignment. The blind was broken after acquisition of all endpoint data for all subjects." (p. 904)
Incomplete outcome data addressed? All outcomes	Unclear	Comment: Reasons for drop-out specified (p. 905), but outcome data were only reported for completers. Of the 45 patients enrolled, 42 completed treatment (13 in fluoxetine group, 16 in olanzapine group, 13 in fluoxetine + olanzapine group) Reasons for early termination: Onset of a number of psychosocial stressors culminating in a suicide gesture: 1/0/0 Dizziness and headaches: 0/0/1 Lost to follow-up: 0/0/1
Free of selective reporting?	Unclear	Comment: Insufficient information to permit judgment of 'Yes' or 'No'
Free of other bias?	Yes	Quote: "Potential subjects were excluded if they [...] were currently being prescribed any psychotropic medication" (p. 904)

Zanarini 2004 (*Continued*)

Bias due to sponsoring improbable?	No	Quote: "Supported by a grant from Eli Lilly, Indianapolis, Ind." (p. 903)

Zanarini 2007

Methods	Design: RCT Allocation: Randomised, no further details Blinding: Double-blind, no further details Duration: 12 weeks (after a 2 weeks screening period) Setting: Outpatient
Participants	Diagnosis: BPD (DSM-IV-TR, DIPD-IV), Zan-BPD total score of 9 or more Age: Mean 32.98 (SD = 10.83) Sex: 332 F, 119 M Exclusions: Bipolar disorder, schizophrenia, major depressive disorder within last 3 months, substance dependence within last 3 months, current PTSD, current panic disorder, current obsessive-compulsive disorder, comorbid Cluster A Axis II PD, active suicidality, pregnancy
Interventions	1. Olanzapine: 2.5 mg/day N = 150 2. Olanzapine: 5 to 10 mg/day, mean dose 6.66 mg/day (SD = 2.91) N = 148 (106 F, 42 M) 3. Placebo: Daily capsules N = 153 (117 F, 36 M)
Outcomes	BPD severity: Number of patients in each group with response/no response, i.e. 50% reduction at least in ZAN-BPD total score Avoidance of abandonment: ZAN-BPD-frantic efforts to avoid abandonment Interpersonal problems: ZAN-BPD unstable interpersonal relationships, SCL-90-R-INT Identity disturbance: ZAN-BPD-identity disturbance Impulsivity: ZAN-BPD-impulsivity, OAS-M-aggression Suicidal ideation: OAS-M-suicidal ideation Suicidal behaviour: ZAN-BPD-suicidal or self-mutilating behaviour Affective instability: ZAN-BPD-affective instability Feelings of emptiness: ZAN-BPD-chronic feelings of emptiness Anger: ZAN-BPD-intense anger, OAS-M-irritability, SCL-90-R-HOS Dissociative symptoms: ZAN-BPD-paranoid ideation of disassociation, SCL-90-R-PAR Depression: MADRS, SCL-90-R-DEP Anxiety: SCL-90-R-ANX General psychiatric pathology: SCL-90-R GSI Mental health status: Sheehan Disability Scale-total, GAF Attrition Adverse effects: Weight, Simpson-Angus Scale, BARS, AIMS
Notes	* As randomised

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "patients were randomised to 1 of 3 treatment groups" (Eli Lilly, 2008, p. 3) Comment: randomisation conducted centrally
Allocation concealment?	Yes	Comment: Probably done, since this RCT was conducted in parallel with the olanzapine flexible-dose trial (Schulz 2008), where a randomisation code was used
Blinding? self-rated outcomes	Yes	Quote: "Double-blind treatment" (Eli Lilly, 2008, p. 1) Comment: Probably equally managed as in Schulz 2008
Blinding? observer-rated outcomes	Yes	Quote: "Double-blind treatment" (Eli Lilly, 2008, p. 1) Comment: Probably equally managed as in Schulz 2008
Incomplete outcome data addressed? All outcomes	Unclear	Quote: "451 were randomly assigned (148 [...] to olanzapine 5-to-10 mg/day treatment group, 150 [...] to olanzapine 2.5-mg/day treatment group, and 153 to placebo)" (Eli Lilly 2008, p. 14), "last observation carried forward" (Eli Lilly 2008, p. 3) Continuous data based on LOCF data Dichotomous data based on ITT sample Of the 451 patients enrolled, 294 completed the full 12 weeks of the double-blind treatment phase (97/103/94) Comment: In this review, only the groups receiving olanzapine 5 to 10 mg/day or placebo group were included.
Free of selective reporting?	Yes	Comment: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review are reported in the pre-specified way.
Free of other bias?	Unclear	Comment: Not specified if there was a washout period or if concomitant psychotropic medication was allowed. Proba-

		bly, medication with primarily CNS activity was not allowed (except for protocol-specified benzodiazepines and hypnotics), as was the case for the Schulz 2007 trial
Bias due to sponsoring improbable?	No	Eli Lilly was the study sponsor. Most study results used here are from the company's study report (the remaining references were either clinical trial register entries or congress abstracts and did not provide detailed data).

*as randomised
ADDS - Atypical Depression Inventory
ADP-IV - Assessment of DSM-IV Personality Disorders
AIAQ - Anger, Irritability, and Assault Questionnaire
AIMS - Abnormal Involuntary Movement Scale
ALS - Affective Lability Scale
AQ - Assault Questionnaire
BARS - Barnes Akathisia Rating Scale
BDHI - Buss-Durkee Hostility Inventory
BID - Beck Depression Inventory
BIS - Barratt Impulsiveness Scale
BPDSI - Borderline Personality Disorder Severity Index
BPRS - Brief Psychiatric Rating Scale
CGI - Clinical Global Impressions Scale
CGI-BPD - Clinical Global Impressions Scale modified for borderline personality disorder
CGI-I Clinical Global Impressions Scale-global improvement
CGI-S Clinical Global Impressions Scale-Severity of Illness
DBT - Dialectical Behaviour Therapy
DES - Dissociative Experiences Scale
DIB - Diagnostic Interview for Borderline Patients
DIB-R - Diagnostic Interview for Borderline Patients-Revised
GAF - Global Assesment of Functioning
GAS - Global Assessment Scale
Ham-D - Hamilton Rating Scale for Depression
HARS - Hamilton Anxiety Rating Scale
HDRS-24 - Hamilton's 24-item Depression Rating Scale
HSCL - Hopkins Symptom Checklist
HSCL-DEP - depression
HSCL-HOS - anger-hostility
HSCL-INT - interpersonal sensitivity
HSCL-PSY - psychotic
IMPS - Inpatient Multidimensional Rating Scale
ITT - intention to treat
LOCF - Last observation carried forward
MADRS - Montgomery-Asberg Depression Rating Scale
MAOI - monoamine oxidase inhibitor agents

MOAS - Modified Overt Aggression Scale
OAS-M - Overt Aggression Scale-Modified
PANSS - Positive and Negative Syndrome Scale
PDRS - Personality Disorder Rating Scale
POMS - Profile of Mood States
SCID-II - Structured Clinical Interview for DSM Axis II Personality Disorders
SCL-90 - Symptom Checklist-90
SCL-90-R - Symptom Checklist-90 - Revised
SCL-90-ANX - anxiety
SCL-90-DEP - depression
SCL-90-GSI - global severity index
SCL-90-HOS - hostiliy
SCL-90-INT - interpersonal sensitivity
SCL-90-PAR - paranoid ideation
SCL-90-PST - positive symptom total
SCL-90-PSY - psychoticism
SIB - Schedule for Interviewing Borderlines
SSI - Schizotypal Symptom Inventory
SSRI - Selective Serotonine Reuptake Inhibitor
STAXI - State-Trait Anger Expression Inventory
STIC - Self Report Test of Impulse Control
TCA - tricyclic antidepressant
ZAN-BPD - Zanarini Rating Scale for Borderline Personality Disorder

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bellino 2005	Allocation: not randomised; open trial
Bellino 2006a	Allocation: not randomised; open trial
Bellino 2006b	Comparison: fluoxetine vs. fluoxetine + Interpersonal Therapy; testing the effects of additional psychotherapy as compared to pharmacotherapy alone
Benedetti 1998	Allocation: not randomised; open trial
Bohus 1999	Allocation: not randomised; open trial
Chengappa 1999	Allocation: not randomised; retrospective chart review
Coccaro 1997	Patients: less than 70% BPD
Cornelius 1990	Allocation: not randomised; open trial
Cornelius 1993	Investigates the effects of continuation therapy in patients of the Soloff 1989 trial, but only responders were allowed to enter this study

(*Continued*)

Cowdry 1988	Randomised cross-over trial, no separate data first period available
Frankenburg 1993	Allocation: not randomised; open trial
Hilger 2003	Allocation: not randomised; case series
Hollander 2005	Data not sufficient for effect size calculation concerning any outcome of interest
Koenigsberg 2003	Participants: less than 70% BPD
La Malfa 2003	Participants: less than 70% BPD; separate data on BPD patients available but not sufficient for effect size calculation
Links 1990	Participants: BPD characteristics, mean DIB score 9.47 (SD = 0.75); exact number of BPD patients unclear Data: no separate data for first arm of cross-over trial (randomised cross-over trial)
Markovitz 1991	Allocation: not randomised; open trial
Markovitz 1995a	Data: not sufficient for effect size calculation
Markovitz 1995b	Allocation: not randomised; open trial
Norden 1989	Allocation: not randomised; open trial
Parsons 1989	Participants: less than 75% BPD; no separate data available
Philipsen 2004a	Intervention: administration in acute dissociative states only, not for continuous treatment
Philipsen 2004b	Allocation: not randomised; open trial Intervention: administered in acute states of aversive inner tension only, not for continuous treatment
Rocca 2002	Allocation: not randomised; open trial
Russell 2003	Participants: PD but not BPD patients
Schulz 1999	Allocation: not randomised; open trial
Serban 1984	Participants: less than 70% BPD
Soloff 1986	Midpoint analysis of the Soloff 1989 trial which has been included
Soloff 1987	Compares haloperidol responders to patients receiving placebo of the Soloff 1989 trial
Verkes 1998	Participants: suicide attempt repeaters, not clear how many patients actually had a BPD
Ziegenhorn 2009	Within-subject crossover-design, no separate data for first study periods available

Characteristics of ongoing studies *[ordered by study ID]*

AstraZen NCT00254748

Trial name or title	The effect of quetiapine on psychotic-like symptoms in borderline personality disordered patients: a randomised placebo-controlled trial
Methods	RCT
Participants	BPD according to DSM-IV, including criterion 9; 18-55 years, in- or outpatients
Interventions	8 weeks of quetiapine (flexible dose between 200 mg/day and 600 mg/day) vs. placebo
Outcomes	Psychotic-like symptoms, severity of psychiatric symptoms; mood, anger, impulsiveness, hostility, anxiety
Starting date	June 2004
Contact information	AstraZeneca Netherlands
Notes	

Bohus NCT00124839

Trial name or title	Evaluation of the efficacy of the opioid antagonist naltrexone on the incidence and intensity of flashbacks and dissociative states in patients with borderline personality disorder
Methods	RCT
Participants	BPD according to DSM-IV, Dissociation Experience Scale (DES) score 25 at least, not actively abusing opiates, no other psychopharmacological treatment for at least two weeks
Interventions	Naltrexone vs. placebo
Outcomes	Reduction of dissociative symptoms, flashbacks, self-injurious behaviour, psychopathology (depression, anxiety, anger, borderline symptoms), safety
Starting date	October 2005
Contact information	Bohus M, Central Institute of Mental Health, Mannheim, Germany
Notes	This study has been terminated in April 2008. (Difficulties in recruiting enough subjects)

Casas NCT00437099

Trial name or title	Efficacy of omega-3 fatty acids on borderline personality disorder: a randomised, double-blind, clinical trial
Methods	RCT
Participants	BPD according to DSM-IV, CGI-S (BPD) > 3, 18-65 years

Casas NCT00437099 (*Continued*)

Interventions	12 weeks of cognitive behaviour therapy (CBT) + placebo vs. CBT + Omacor (R) 1680 mg/day vs. CBT + Omacor (R) 3360 mg/day
Outcomes	Depression, manic symptoms, impulsivity, aggression, anger, psychotic symptoms, anxiety, suicidal and parasuicidal behaviour, adverse events
Starting date	Unknown
Contact information	Casa M, Hospital Univesitari Vall d'Hebron, Barcelona, Spain
Notes	

Goodman NCT00255554

Trial name or title	Effects of Dialectical Behavioural Therapy and escitalopram on impulsive aggression, affective instability and cognitive processing in borderline personality disorder
Methods	RCT
Participants	BPD, 18-60 years, off psychotropic medication for at least 2 weeks
Interventions	Six months of DBT + escitalopram vs. DBT + placebo
Outcomes	Impulsivity, aggression, affective impulsivity, immediate and delayed memory, cognitive processing
Starting date	November 2005
Contact information	Goodman M, Bronx VA Medical Center, New York, USA
Notes	

Malev ISRCTN11135486

Trial name or title	Quetiapine versus sertraline as the pharmacological component in a standardised psychopharmacological and psychotherapeutic treatment of borderline personality disorder: a randomised, rater-blinded study
Methods	RCT
Participants	BPD according to DSM-IV, females, at least 18 years of age
Interventions	24 weeks of quetiapine (50-800 mg/day) vs. sertraline (25-200 mg/day)
Outcomes	Anger, hostility, severity of affective symptoms, anxiety, depression, psychotic symptoms, interpersonal problems, duration of hospitalisation, co-medication
Starting date	October 2006

Malev ISRCTN11135486 (*Continued*)

Contact information	Malevani J, University of Düsseldorf, Germany
Notes	

Ralevski NCT00463775

Trial name or title	Topiramate for treatment of patients with borderline personality disorder and alcohol dependence
Methods	RCT
Participants	BPD and alcohol dependence, 21-60 years
Interventions	8 weeks of topiramate (250 mg/day) vs. placebo
Outcomes	Hostility, aggression, drinking, craving, side effects
Starting date	March 2007
Contact information	Ralevski E, Yale University, USA
Notes	

Schulz NCT00222482

Trial name or title	A double-blind and placebo controlled assessment of Depakote ER in borderline personality disorder
Methods	RCT
Participants	BPD, 21-55 years
Interventions	12 weeks of DBT + Depakote ER vs. DBT + placebo
Outcomes	SCL-90, impulsivity
Starting date	March 2003
Contact information	Schulz SC, University of Minnesota Medical School, USA
Notes	

DATA AND ANALYSES

Comparison 1. Active drug versus placebo: BPD severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.22, 0.82]
1.2 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.98, 0.05]
1.3 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.65, 0.35]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.28 [-0.28, 0.83]
3 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	2	596	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.41, 0.10]
3.2 Mood stabilizers: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-1.20, 0.34]

Comparison 2. Active drug versus placebo: Avoidance of abandonment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.58, 0.43]
2 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.22, 0.21]

Comparison 3. Active drug versus placebo: Interpersonal problems

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.33, -0.20]
1.3 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.63, 0.38]
1.4 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.46, 0.38]
1.5 Mood stabiliser: Valproate semisodium	1	30	Std. Mean Difference (IV, Random, 95% CI)	-1.04 [-1.85, -0.23]
1.6 Mood stabiliser: Topiramate	1	56	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.46, -0.35]
1.7 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.92, 0.13]
1.8 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.26, 0.74]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.74, 0.37]
3 SMD on basis of change from baseline scores	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	2	340	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.31, 0.12]
4 Mean Change Difference	1		MCD (Random, 95% CI)	Subtotals only
4.1 Second-generation antipsychotics: Olanzapine	1	291	MCD (Random, 95% CI)	-0.2 [-0.62, 0.22]

Comparison 4. Active drug versus placebo: Identity disturbance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.90, 0.13]
2 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.21, 0.10]

Comparison 5. Active drug versus placebo: Impulsivity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	13		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.30, 0.43]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-1.84 [-2.49, -1.18]
1.3 Second-generation antipsychotics: Olanzapine	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.54, 0.47]
1.4 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.48, 0.53]
1.5 Mood stabiliser: Valproate semisodium	2	46	Std. Mean Difference (IV, Random, 95% CI)	-0.62 [-1.48, 0.24]
1.6 Mood stabiliser: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-1.62 [-2.54, -0.69]
1.7 Mood stabiliser: Topiramate	2	71	Std. Mean Difference (IV, Random, 95% CI)	-3.36 [-4.44, -2.27]
1.8 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.64, 0.40]
1.9 Antidepressants: Fluoxetine	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.50, 0.31]
1.10 Antidepressants: Fluvoxamine	1	38	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.68, 0.59]
1.11 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.50, 0.50]
1.12 Miscellaneous: Omega-3 fatty acids	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-1.28, 0.34]
2 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	2	340	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.40, 0.03]
2.2 Mood stabilizers: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-1.41 [-2.27, -0.55]
3 Mean Change Difference	1		MCD (Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	1	291	MCD (Random, 95% CI)	-0.10 [-0.40, 0.20]
4 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mood stabiliser: Carbamazepine	1	20	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.53, 1.46]

Comparison 6. Active drug versus placebo: Suicidal ideation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.78, 0.23]
1.2 Mood stabiliser: Valproate semisodium	1	16	Std. Mean Difference (IV, Random, 95% CI)	0.52 [-0.63, 1.67]
1.3 Antidepressants: Fluoxetine	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.44 [-0.46, 1.33]
2 SMD on basis of change from baseline scores	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	2	340	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [0.07, 0.50]
3 Mean Change Difference	1		MCD (Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	1	291	MCD (Random, 95% CI)	-0.1 [-0.20, -0.00]
4 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Second-generation antipsychotics versus placebo: Olanzapine	1	24	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.50, 2.88]
4.2 Miscellaneous: Omega-3 fatty acids	1	49	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.28, 0.95]

Comparison 7. Active drug versus placebo: Suicidal behaviour

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Flupenthixol decanoate	1	37	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.26, 0.92]
1.2 Antidepressants: Mianserin	1	58	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.71, 1.41]
2 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.36, 0.65]

Comparison 8. Active drug versus placebo: Self-mutilating behaviour

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Aripiprazole	1	52	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.25]
1.2 Second-generation antipsychotics: Olanzapine	1	24	Risk Ratio (M-H, Random, 95% CI)	1.2 [0.50, 2.88]
1.3 Miscellaneous: Omega-3 fatty acids	1	49	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.51, 2.97]
2 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Antidepressants: Fluoxetine	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.85, 0.92]

Comparison 9. Active drug versus placebo: Affective instability

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.61, 0.41]
1.2 Antidepressants: Fluvoxamine	1	38	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.30, 0.01]
2 SMD on basis of change from baseline scores	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.32, -0.01]
2.2 Mood stabilizers: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.61 [-1.39, 0.17]

Comparison 10. Active drug versus placebo: Chronic feelings of emptiness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.32, 0.69]
2 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.22, 0.16]

Comparison 11. Active drug versus placebo: Anger

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	13		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.84, -0.09]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-1.14 [-1.73, -0.55]
1.3 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.43, 0.58]
1.4 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-1.25, 0.57]
1.5 Mood stabiliser: Valproate semisodium	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.91, 0.61]
1.6 Mood stabiliser: Valproate semisodium	1	16	Std. Mean Difference (IV, Random, 95% CI)	-1.83 [-3.17, -0.48]
1.7 Mood stabiliser: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-1.69 [-2.62, -0.75]
1.8 Mood stabiliser: Topiramate (females)	2	85	Std. Mean Difference (IV, Random, 95% CI)	-1.00 [-3.64, -2.36]
1.9 Mood stabiliser: Topiramate (males)	1	42	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.27, -0.03]
1.10 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.78, 0.26]
1.11 Antidepressants: Fluoxetine	1	22	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.53, 0.22]
1.12 Antidepressants: Fluvoxamine	1	38	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-1.01, 0.28]
1.13 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.84, 0.17]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.63, 0.48]
3 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.43, -0.12]

Comparison 12. Active drug versus placebo: Psychotic symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-1.09, 0.20]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-1.64, -0.47]
1.3 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.74, 0.28]
1.4 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.50, 0.35]
1.5 Mood stabiliser: Topiramate	1	56	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.02, 0.05]
1.6 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.96, 0.09]
1.7 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.78, 0.22]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.37, 0.75]
3 SMD on basis of change from baseline scores	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	3	631	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.34, -0.03]

Comparison 13. Active drug versus placebo: Dissociation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Antidepressants: Fluoxetine	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.42 [-0.47, 1.32]

Comparison 14. Active drug versus placebo: Depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	13		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.87, 0.68]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-1.25 [-1.85, -0.65]
1.3 Second-generation antipsychotics: Olanzapine	2	84	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.80, 0.07]
1.4 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.81, 0.21]
1.5 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.59, 0.27]
1.6 Mood stabiliser: Valproate semisodium	2	46	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.31, -0.01]
1.7 Mood stabiliser: Topiramate	1	56	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.04, 0.02]
1.8 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.12, -0.06]
1.9 Antidepressant: Fluoxetine	2	42	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-1.13, 1.36]
1.10 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.84, 0.16]
1.11 Miscellaneous: Omega-3 fatty acids	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-1.15, 0.46]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.43, 0.68]
3 Mean Change Difference	2		MCD (Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	2	596	MCD (Random, 95% CI)	0.39 [-0.20, 0.97]
4 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Miscellaneous: Omega-3 fatty acid	1	49	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.28, 0.81]

Comparison 15. Active drug versus placebo: Anxiety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.68, 0.79]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.29, -0.17]

1.3 Second-generation antipsychotics: Olanzapine	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.74, 0.28]
1.4 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.63, 0.39]
1.5 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.43, 0.41]
1.6 Mood stabiliser: Topiramate	1	56	Std. Mean Difference (IV, Random, 95% CI)	-1.40 [-1.99, -0.81]
1.7 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.67, 0.37]
1.8 Antidepressants: Fluoxetine	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.73, 1.03]
1.9 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.65, 0.36]
2 Mean Change Difference	1		MCD (Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	1	274	MCD (Random, 95% CI)	-0.22 [-0.41, -0.03]

Comparison 16. Active drug versus placebo: General psychiatric pathology

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.71, 0.54]
1.2 Second-generation antipsychotics: Aripiprazole	1	52	Std. Mean Difference (IV, Random, 95% CI)	-1.27 [-1.87, -0.67]
1.3 Second-generation antipsychotics: Ziprasidone	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.92, 0.10]
1.4 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-1.49, 0.36]
1.5 Mood stabiliser: Topiramate	1	56	Std. Mean Difference (IV, Random, 95% CI)	-1.19 [-1.76, -0.61]
1.6 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.87, 0.18]
1.7 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.73, 0.27]
2 SMD on basis of change from baseline scores	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Second-generation antipsychotics: Olanzapine	2	557	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.53, 0.10]

Comparison 17. Active drug versus placebo: Mental health status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	2	114	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.77, 1.08]
1.2 Second-generation antipsychotics: Olanzapine	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.53, 0.48]
1.3 Mood stabiliser: Carbamazepine	1	19	Std. Mean Difference (IV, Random, 95% CI)	0.34 [-0.57, 1.25]
1.4 Antidepressants: Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.25, 0.79]
1.5 Antidepressants: Fluoxetine	2	42	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.27, 1.07]
1.6 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.36, 0.64]
2 SMD on basis of post-means and pre-SDs	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 First-generation antipsychotics: Thiothixene	1	50	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.50, 0.61]
3 Mean Change Difference	2		MCD (Random, 95% CI)	Subtotals only
3.1 Second-generation antipsychotics: Olanzapine	2	596	MCD (Random, 95% CI)	1.52 [-0.75, 3.79]
4 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Mood stabiliser: Valproate semisodium	1	16	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.37, 1.11]

Comparison 18. Active drug versus placebo: Attrition/leaving the study early for any reason

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	24		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Flupenthixol decanoate	1	37	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.36, 5.43]
1.2 First-generation antipsychotics versus placebo: Haloperidol	2	130	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.45, 2.92]
1.3 First-generation antipsychotics versus placebo: Thiothixene	1	50	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.74, 8.68]
1.4 Second-generation antipsychotics: Olanzapine	6	767	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.72, 1.29]
1.5 Second-generation antipsychotics: Ziprasidone	1	60	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.74, 1.99]

1.6 Mood stabiliser: Carbamazepine	1	20	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.27, 92.62]
1.7 Mood stabiliser: Valproate semisodium	2	46	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.40, 1.53]
1.8 Mood stabiliser: Lamotrigine	2	55	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.22, 2.48]
1.9 Mood stabiliser: Topiramate	3	133	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.14, 2.16]
1.10 Antidepressants: Amitriptyline	1	59	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 14.74]
1.11 Antidepressants: Fluoxetine	1	25	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.33, 8.11]
1.12 Antidepressants: Fluvoxamine	1	38	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.04, 4.55]
1.13 Antidepressants: Mianserin	1	58	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.72, 3.12]
1.14 Antidepressants: Phenelzine sulfate	1	72	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.18, 1.94]
1.15 Miscellaneous: Omega-3 fatty acids	2	79	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.79]

Comparison 19. Active drug versus placebo: AE - body weight change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 First-generation antipsychotics: Haloperidol	1	58	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.70, 0.34]
1.2 Second-generation antipsychotics: Olanzapine	6	752	Std. Mean Difference (IV, Random, 95% CI)	1.05 [0.90, 1.20]
1.3 Mood stabiliser: Valproate semisodium	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.68 [-0.10, 1.47]
1.4 Mood stabiliser: Lamotrigine	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.93, 0.67]
1.5 Mood stabilizer: Topiramate	3	127	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.91, -0.19]
1.6 Antidepressants: Phenelzine sulfate	1	62	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.39, 0.61]

Comparison 20. Active drug versus placebo: AE - any AE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics versus placebo: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.00, 1.28]
1.2 Second-generation antipsychotics versus placebo: Ziprasidone	1	60	Risk Ratio (M-H, Random, 95% CI)	2.75 [0.99, 7.68]

Comparison 21. Active drug versus placebo: AE - increased appetite

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	2.76 [1.75, 4.34]

Comparison 22. Active drug versus placebo: AE - paraesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 27.12]

Comparison 23. Active drug versus placebo: AE - headache

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.43, 1.92]
1.2 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.61]

Comparison 24. Active drug versus placebo: AE - dizziness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics versus placebo: Ziprasidone	1	60	Risk Ratio (M-H, Random, 95% CI)	9.00 [0.51, 160.17]
1.2 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.27, 8.30]

Comparison 25. Active drug versus placebo: AE - disturbance in attention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	1	301	Risk Ratio (M-H, Random, 95% CI)	11.37 [0.63, 203.81]
1.2 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.55, 7.22]

Comparison 26. Active drug versus placebo: AE - memory problems

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.55, 7.22]

Comparison 27. Active drug versus placebo: AE - fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.79, 5.23]
1.2 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.40, 10.05]

Comparison 28. Active drug versus placebo: AE - somnolence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	2.97 [1.75, 5.03]

Comparison 29. Active drug versus placebo: AE - sedation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine (1)	1	314	Risk Ratio (M-H, Random, 95% CI)	9.23 [2.18, 39.12]
1.2 Second-generation antipsychotics: Olanzapine (2)	1	28	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.44, 3.66]
1.3 Second-generation antipsychotics versus placebo: Ziprasidone	1	60	Risk Ratio (M-H, Random, 95% CI)	6.0 [0.77, 46.87]

Comparison 30. Active drug versus placebo: AE - insomnia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.33, 1.37]

Comparison 31. Active drug versus placebo: AE - anxiety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	1	314	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.33, 2.42]

Comparison 32. Active drug versus placebo: AE - nausea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.43, 1.59]

Comparison 33. Active drug versus placebo: AE - uneasy feeling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics versus placebo: Ziprasidone	1	60	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.38, 129.93]

Comparison 34. Active drug versus placebo: AE - constipation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics versus placebo: Olanzapine	1	28	Risk Ratio (M-H, Random, 95% CI)	6.5 [0.41, 104.20]

Comparison 35. Active drug versus placebo: AE - dry mouth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	615	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.08, 4.67]

Comparison 36. Active drug versus placebo: AE - nasopharyngitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	1	301	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.23, 1.66]

Comparison 37. Active drug versus placebo: AE - menstrual pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Risk Ratio	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Mood stabiliser: Topiramate	1	56	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.44, 6.31]

Comparison 38. Active drug versus placebo: AE - liver function: AST/SGOT baseline to endpoint mean change (U/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	2	526	Std. Mean Difference (IV, Random, 95% CI)	0.35 [0.18, 0.52]

Comparison 39. Active drug versus placebo: AE - liver function: ALT/SGPT baseline to endpoint mean change (U/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	530	Std. Mean Difference (IV, Random, 95% CI)	0.46 [0.29, 0.63]

Comparison 40. Active drug versus placebo: AE - liver function: GGT (GGPT/SGGT/YGGT) baseline to endpoint mean change (U/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	268	Std. Mean Difference (IV, Random, 95% CI)	0.26 [0.02, 0.50]

Comparison 41. Active drug versus placebo: AE - liver function: total bilirubin baseline to endpoint mean change (μmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	264	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.53, -0.05]

Comparison 42. Active drug versus placebo: AE - liver function: direct bilirubin baseline to endpoint mean change (μmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	258	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.60, -0.11]

Comparison 43. Active drug versus placebo: AE - lipids: total cholesterol baseline to endpoint change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotics: Olanzapine	2	327	Std. Mean Difference (IV, Random, 95% CI)	0.42 [0.20, 0.64]

Comparison 44. Active drug versus placebo: AE - lipids: LDL cholesterol baseline to endpoint mean change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	259	Std. Mean Difference (IV, Random, 95% CI)	0.35 [0.10, 0.59]

Comparison 45. Active drug versus placebo: AE - lipids: HDL cholesterol (dextran precip.) baseline to endpoint mean change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.52, -0.04]

Comparison 46. Active drug versus placebo: AE - lipids: triglycerides, fasting, baseline to endpoint mean change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	203	Std. Mean Difference (IV, Random, 95% CI)	0.37 [0.09, 0.64]

Comparison 47. Active drug versus placebo: AE - prolactin: baseline to endpoint mean change (μg/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	2	528	Std. Mean Difference (IV, Random, 95% CI)	0.41 [0.23, 0.59]

Comparison 48. Active drug versus placebo: AE - platelet count baseline to endpoint mean change (GI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	2		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Second-generation antipsychotic: Olanzapine	2		Std. Mean Difference (IV, Random, 95% CI)	Not estimable

Comparison 49. Active drug versus placebo: AE - erythrocyte count baseline to endpoint mean change (TI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.42, 0.06]

Comparison 50. Active drug versus placebo: AE - leukocyte count baseline to endpoint mean change (GI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.65, -0.16]

Comparison 51. Active drug versus placebo: AE - neutrophils, segmented, baseline to endpoint mean change (GI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.63, -0.14]

Comparison 52. Active drug versus placebo: AE - basophils baseline to endpoint mean change (GI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.53, -0.04]

Comparison 53. Active drug versus placebo: AE - monocytes baseline to endpoint mean change (GI/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.53, -0.04]

Comparison 54. Active drug versus placebo: AE - haemoglobin baseline to endpoint mean change (mml/L-F)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	262	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]

Comparison 55. Active drug versus placebo: AE - mean cell haemoglobin concentration (MCHC) baseline to endpoint mean change (mml/L-F)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	260	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.22, 0.27]

Comparison 56. Active drug versus placebo: AE - calcium baseline to endpoint mean change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	268	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.57, -0.09]

Comparison 57. Active drug versus placebo: AE - albumin baseline to endpoint mean change (g/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]

Comparison 58. Active drug versus placebo: AE - creatine phosphokinase baseline to endpoint mean change (U/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	268	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.45, 0.03]

Comparison 59. Active drug versus placebo: AE - urea nitrogen baseline to endpoint mean change (mmol/L)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	269	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.38, 0.10]

Comparison 60. Active drug versus placebo: AE - pulse, standing, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.15, 0.31]

Comparison 61. Active drug versus placebo: AE - pulse, supine, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.21, 0.25]

Comparison 62. Active drug versus placebo: AE - diastolic blood pressure, standing, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.26, 0.20]

Comparison 63. Active drug versus placebo: AE - diastolic blood pressure, supine, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.24, 0.22]

Comparison 64. Active drug versus placebo: AE - systolic blood pressure, standing, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.20, 0.26]

Comparison 65. Active drug versus placebo: AE - systolic blood pressure, supine, baseline to endpoint mean change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SMD	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Second-generation antipsychotic: Olanzapine	1	290	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.27, 0.19]

Comparison 66. Drug versus drug: BPD severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.46 [-0.03, 0.96]

Comparison 67. Drug versus drug: Interpersonal problems

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol vs. Amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.66, 0.38]
1.2 Haloperidol vs. Phenelzine Sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.96, 0.04]

Comparison 68. Drug versus drug: Impulsivity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	0.20 [-0.32, 0.72]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.40, 0.58]
2 Second-generation antipsychotic versus antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Olanzapine versus fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.93, 0.53]

Comparison 69. Drug versus drug: Anger

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.89, 0.16]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.41, 0.57]

Comparison 70. Drug versus drug: Psychotic symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.87, 0.18]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.34, 0.64]

Comparison 71. Drug versus drug: Depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.44, 0.59]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.68 [0.17, 1.19]
2 Second-generation antipsychotic versus antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Olanzapine versus fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.49, 0.03]

Comparison 72. Drug versus drug: Anxiety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.70, 0.34]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.15, 1.16]

Comparison 73. Drug versus drug: General psychiatric pathology

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.59, 0.45]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	0.53 [0.03, 1.03]

Comparison 74. Drug versus drug: Mental health status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus amitriptyline	1	57	Std. Mean Difference (IV, Random, 95% CI)	0.29 [-0.23, 0.81]
1.2 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.01, -0.01]

Comparison 75. Drug versus drug: AE - attrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.46, 2.85]
2 First-generation antipsychotic versus antidepressant	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Haloperidol versus amitriptyline	1	61	Risk Ratio (M-H, Random, 95% CI)	2.90 [0.32, 26.38]
2.2 Haloperidol versus phenelzine sulfate	1	74	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.49, 5.15]
3 Second-generation antipsychotic versus antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.69]

Comparison 76. Drug versus drug: AE - body weight change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Haloperidol versus phenelzine sulfate	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.78, 0.21]
2 Second-generation antipsychotic versus antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

2.1 Olanzapine versus fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	0.98 [0.20, 1.76]

Comparison 77. Drug versus drug: AE - any AE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.66, 2.45]

Comparison 78. Drug versus drug: AE - sedation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Random, 95% CI)	3.5 [1.23, 9.92]

Comparison 79. Drug versus drug: AE - sleepiness/drowsiness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.23, 2.76]

Comparison 80. Drug versus drug: AE - restlessness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.26, 8.50]
2 Second-generation antipsychotic versus antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Olanzapine versus fluoxetine	1	30	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.23, 2.11]

Comparison 81. Drug versus drug: AE - muscle spasms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.33, 27.63]

Comparison 82. Drug versus drug: AE - fainting spells

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 First-generation antipsychotic versus first-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loxapine versus chlorpromazine	1	80	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.68]

Comparison 83. Drug versus combination of drugs: Impulsivity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.71, 0.76]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Fluoxetine versus fluoxetine + olanzapine	1	26	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.53, 1.02]

Comparison 84. Drug versus combination of drugs: Depression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [1.00, 0.47]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Fluoxetine versus fluoxetine + olanzapine	1	26	Std. Mean Difference (IV, Random, 95% CI)	0.54 [-0.24, 1.33]

Comparison 85. Drug versus combination of drugs: AE - attrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	31	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.01, 3.63]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

2.1 Fluoxetine versus fluoxetine + olanzapine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.05, 5.28]

Comparison 86. Drug versus combination of drugs: AE - body weight change

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	29	Std. Mean Difference (IV, Random, 95% CI)	0.70 [-0.05, 1.46]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Fluoxetine versus fluoxetine + olanzapine	1	26	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-1.32, 0.25]

Comparison 87. Drug versus combination of drugs: AE - sedation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	31	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.87, 2.96]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Fluoxetine versus fluoxetine + olanzapine	1	29	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.15, 1.44]

Comparison 88. Drug versus combination of drugs: AE - akathisia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Second-generation antipsychotic versus second-generation antipsychotic + antidepressant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Olanzapine versus olanzapine + fluoxetine	1	31	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.25, 2.28]
2 Antidepressant versus antidepressant + second-generation antipsychotic	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Fluoxetine versus fluoxetine + olanzapine	1	29	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.39, 2.92]

WHAT'S NEW

Last assessed as up-to-date: 24 January 2010.

Date	Event	Description
10 May 2010	New citation required but conclusions have not changed	Substantive amendment undertaken by a new author team
10 May 2010	New search has been performed	This is an update of the review of the same title published first in 2006

HISTORY

Review first published: Issue 1, 2006

Date	Event	Description
30 April 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Jutta Stoffers: wrote protocol and final report, selected studies, obtained papers, extracted data, entered data.

Birgit Völlm: helped write the protocol and final report, selected studies, obtained papers, extracted data, entered data.

Gerta Rücker: helped write the protocol and final report, gave statistical support and helped extract data.

Antje Timmer: helped write the protocol, corrected final report.

Nick Huband: helped examine literature search retrievals.

Klaus Lieb: sought funds, helped write the protocol, revised final report.

DECLARATIONS OF INTEREST

We are not aware of any personal, political, academic or financial conflicts. KL was involved in the Schulz 2007 trial by recruiting and assessing participants as one of the 39 study sites. KL and JS have been involved in the process of preparation of the WFSBP guidelines for the treatment of personality disorders (Herpertz 2007). KL has not received any payments from industry since the beginning of 2007 to avoid any kind of conflicts of interest. We are not aware of any secondary or personal interests.

SOURCES OF SUPPORT

Internal sources

- Research Committee of the University Hospital Freiburg, Germany.

External sources

- German Federal Ministry of Education and Research, grant no. 01KG0609, Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because of the deficiency in numbers of study effects per comparison, we did not perform sensitivity analyses as planned, nor was it possible to draw funnel plots.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [therapeutic use]; Antipsychotic Agents [adverse effects; *therapeutic use]; Borderline Personality Disorder [*drug therapy; psychology]; Fatty Acids, Omega-3 [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans