BEST in Mental Health

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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

In adults with borderline personality disorder how effective is antipsychotic medication compared to any other intervention in achieving improved patient outcomes?

Clarification of question using PICO structure

Patients:	Adults with borderline personality disorder
Intervention:	Antipsychotic medication
Comparator:	Any comparison
Outcome:	Any patient outcomes

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Clinical and research implications

No definite clinical implications can be made from the available evidence. There is, however, some evidence to suggest that anti-psychotics, particularly second-generation anti-psychotics, are effective in treating patients with borderline personality disorder (BPD). The authors of a Cochrane systematic review found that there was no evidence that any drug reduces overall BPD, but found that different treatments were effective in different ways. As such, they recommended that pharmacotherapeutic treatment of BPD should be targeted at defined symptoms. Interestingly, none of the treatments evaluated in the systematic review had any effect on avoidance of abandonment, chronic feelings of emptiness, identity disturbance, and dissociation.

In the systematic review, there was some evidence to suggest that taking olanzapine may have increased self-harming behaviour, and in all studies, it was consistently associated with weight gain. Study authors have advised that doctors and patients need to discuss the potential efficacy of olanzapine relative to potential risks of weight gain. It was also recommended that while no differences were found between patients treated with olanzapine and placebo for glucose or lipids, close monitoring of these metabolic parameters (in addition to weight changes) needs to be done. Another study that evaluated the effectiveness of different doses of olanzapine, suggested that future studies might use a starting dose of 5 mg/d or, if starting at 2.5 mg/d, ensure titration to at least 5 mg/d.

It was also stated that increases in adverse events, such as extrapyramidal side effects with typical antipsychotics, and increased risk of metabolic problems by atypical ones, especially in long-term managements, necessitates sensible precaution with respect to curative plans and impending adverse effects.

There is a concern that given the widespread usage of anti-psychotics for BPD, there is a lack of good quality trials with large numbers of patients to support its use. More studies are needed to replicate the findings from the current studies. The authors of the SR also suggested that it would be desirable to have a consensus on a minimum set of therapy outcome variables that are most likely to be of interest for any BPD patient, and that these outcomes should be more specific and sensitive to BPD relevant pathology. Moreover, future studies should assess adverse events in a more standardised manner.

What does the evidence say?

Number of included studies/reviews (number of participants)
One systematic review (SR) (Stoffers et al. 2010) and two randomised controlled trials (RCTs) (Shafti *et al.* 2010; Zanarini *et al*. 2011) met the inclusion criteria for this BEST summary.

Main Findings
One Cochrane review (Stoffers *et al*. 2010) found improvements in pathology related outcomes for the first-generation antipsychotics flupenthixol, and haloperidol, when compared to placebo, but not for thiothixene. Overall, however, these data were sparse. The authors also found significant effects in pathology related outcomes for second-generation antipsychotics, including aripiprazole, and

olanzapine vs. placebo, but not for ziprasidone. Very little adverse event data were available, except for olanzapine. Patients taking this treatment had a possible increase in self-harming behaviour, significant weight gain, sedation and changes in haemogram parameters. Four RCTs were included that compared a first- or second-generation antipsychotic versus another drug: loxapine versus chlorpromazine, haloperidol versus amitriptyline, haloperidol versus phenelzine sulfate, and olanzapine versus fluoxetine. For the first comparison, there were no usable data available regarding any pathology related outcome, and for the second and last comparisons, there were also no significant differences, with the exception that olanzapine which showed more weight gain and sedation than fluoxetine. Phenelzine sulphate was found to be superior to haloperidol in reducing depression, anxiety, general psychiatric pathology, and improving the overall mental health status. 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.

Two RCTs evaluating olanzapine were published after the above SR. One compared olanzapine vs. placebo in 451 outpatients aged 18–65 years with BPD (Zanarini *et al*. 2011). In this trial, one group received olanzapine 2.5 mg/d (n = 150), another received olanzapine 5–10 mg/d (n = 148), and another received a placebo (n = 153). For the primary outcome, the olanzapine 5- to 10-mg/d group showed a statistically significantly greater mean baseline-to-endpoint decrease in the Zanarini Rating Rating Scale for Borderline Personality Disorder [ZAN-BPD total score] relative to the placebo group ($p = 0.010$); this significant difference was not observed for the lower dose group. Both dose levels were superior to placebo in terms of improved family functioning. Moderate-dose olanzapine was also superior to placebo in improving work/school achievement, and low-dose olanzapine improved social functioning significantly more than placebo. Both doses of olanzapine were significantly associated with decreased reductions in suicidality, as measured using the Overt Aggression Scale-Modified (OAS-M) suicidality score. Treatment-emergent adverse events reported significantly more frequently among olanzapine-treated patients included somnolence, fatigue, increased appetite, and weight increase (all $p < 0.05$).

One double-blind RCT published after the above SR compared the effectiveness of olanzapine versus haloperidol in 28 female patients with BPD (Shafti *et al*. 2010). After eight weeks, both treatments improved patient outcomes (Brief Psychiatric Rating Scale [BPRS], Clinical Global Impression Severity scale [CGI-S], and the Buss-Durkee Hostility Inventory [BDHI]) compared to baseline, but no significant differences were observed between the treatment groups. The authors reported that the side effects were mild and well-tolerated.

Authors Conclusions

The authors of the systematic review (Stoffers *et al*. 2010) concluded that the available evidence indicates some beneficial effects with second-generation antipsychotics – as well as mood stabilisers, and dietary supplementation by omega-3 fatty acids. However, the results are mostly based on single study effect estimates. The authors also stated that 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).

Zanarini *et al*. (2011) concluded that olanzapine 5–10 mg/d showed a clinically modest advantage over placebo in the treatment of overall borderline psychopathology. The authors also cautiously noted that this advantage in effectiveness should be weighed against the risk of adverse events, particularly weight gain.

Shafti *et al.* (2010) concluded that there seems to be no significant difference between olanzapine and haloperidol concerning management of mental and behavioural symptoms of patients with BPD.

Reliability of conclusions/Strength of evidence

The SR by Stoffers *et al*. (2010) was well-conducted, and their cautious conclusions accurately reflect the limited evidence.

In the RCTs by Zanarini *et al*. (2011) and Shafti *et al.* (2010), aspects of trial methodology were not well-reported (e.g. method of randomisation and allocation concealment), but other aspects were well conducted. In the Shafti *et al.* (2100) trial, however, the authors stated that the study was limited by a small sample size and a short duration, thus this study was considered to have a high risk of bias.

What do guidelines say?

NICE clinical guideline CG78 (4) finds insufficient evidence to suggest that antipsychotic medication should be used in the treatment of borderline personality disorder, nor meaningful data assessing the potential harm arising from this treatment. The guideline also states that antipsychotics should not be used in the medium or long-term management of borderline personality disorder.

Date question received: 26/04/2014
Date searches conducted: 30/04/2014
Date answer completed: 02/06/2014

References

1. Shoja, S. Shahveisi B (2010). "Olanzapine versus haloperidol in the management of borderline personality disorder: A randomized double-blind trial." Journal of Clinical Psychopharmacology 30(1): 44-47.
2. Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological interventions for borderline personality disorder. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD005653. (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005653.pub2/pdf)
3. Zanarini, C., et al. (2011). "A dose comparison of olanzapine for the treatment of borderline personality disorder: A 12-week randomized, double-blind, placebo-controlled study." Journal of Clinical Psychiatry 72(10): 1353-136.
4. National Institute for Health and Clinical Excellence. Borderline Personality Disorder: Treatment and Management (2009). The British Psychological Society and The Royal College of Psychiatrists.

Results

Systematic Reviews

Author (year)	Search Date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Stoffers (2010)	2009	**Study design:** A systematic review of randomised controlled trials. **Population:** Adult patients with a formal diagnosis (DSM criteria) of borderline personality disorder. **Intervention:** Any medication or combination of medications with the expressed purpose of treating BPD symptoms. **Comparison:** 4 comparisons were considered a. Placebo b. Active comparator medications c. Combination of medications d. Combined treatment (i.e. DBT) **Outcomes:** Primary outcomes of: a. Overall BPD severity. b. Severity of single BPD criteria according to DSM Secondary outcomes of: a. Depression. b. Anxiety. c. General psychiatric pathology: comprehensive measures.	28 trials (n= 1742)	**Drug vs. placebo:** 4 RCTs were included that evaluated first-generation antipsychotics vs. placebo (thiothixene, flupenthixol, or haloperidol). ***Haloperidol*** had a significant effect concerning the reduction of **anger** (SMD -0.46, N = 114, 2 RCTs, 95% CI -0.84 to -0.09, I2 = 0%), and ***flupenthixol*** treated patients were significantly less likely to get engaged in **suicidal acts** (RR of suicidal behaviour 0.49, N = 37, 1 RCT, 95% CI 0.26 to 0.92). No proof of efficacy was found for ***thiothixene***. 8 RCTs were included that evaluated second-generation antipsychotics vs. placebo (aripiprazole, olanzapine, ziprasidone). Of the second-generation antipsychotics, ***aripiprazole*** had significant effects in the reduction of **interpersonal problems** (SMD -0.77, N = 52, 1 RCT, 95% CI -1.33 to -0.20), **impulsivity** (N = 52, 1 RCT, SMD -1.84, 95% CI -2.49 to -1.18), **anger** (SMD -1.14, N = 52,	Low

		d. Mental health status. e. Attrition. f. Adverse effects.		1 RCT, 95% CI -1.73 to -0.55), **psychotic paranoid symptoms** (SMD -1.05, N = 52, 1 RCT, 95% CI -1.64 to -0.47), **depression** (SMD -1.25, N = 52, 1 RCT, 95% CI -1.85 to -0.65), **anxiety** (SMD -0.73, N = 52, 1 RCT, 95% CI -1.29 to -0.17), and **general psychiatric pathology** (SMD -1.27, N = 52, 1 RCT, 95% CI -1.87 to -0.67). For ***olanzapine***, no significant effects were found for any pathology related outcome in primary analyses. Secondary analyses indicated significant decreases in **affective instability** (mean change SD -0.16, N = 631, 3 RCTs, 95% CI -0.32 to -0.01, I2 = 0%), **anger** (mean change SD -0.27, N = 631, 3 RCTs, 95% CI -0.43 to -0.12, I2 = 0%), **psychotic paranoid symptoms** (mean change SD -0.18, N = 631, 3 RCTs, 95% CI -0.34 to -0.03, I2 = 0%), and **anxiety** (mean change difference -0.22, N = 274, 1 RCT, 95% CI -0.41 to -0.03). 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. 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. **Drug vs. drug**: 4 RCTs were included that compared a first- or second-generation antipsychotic versus another drug. Concerning the comparison of **loxapine versus chlorpromazine**, there were no usable data available regarding any pathology related outcome. **Haloperidol and** the antidepressant **amitriptyline** did not differ significantly concerning any outcome. **Phenelzine sulfate** proved to be superior to **haloperidol** in reducing 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 improving the overall mental health status (SMD -0.51, N = 64, 95% CI -1.01 to -0.01). No significant differences were found for the comparison of the **olanzapine** with the antidepressant **fluoxetine** for any pathology related outcome. 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. **Active drug vs. combination of drugs**: Two RCTs compared active drug vs. combination of drugs: second-generation antipsychotic versus second-generation antipsychotic plus antidepressant (olanzapine versus olanzapine plus fluoxetine), and antidepressant versus antidepressant plus second-generation antipsychotic (fluoxetine versus fluoxetine plus olanzapine). For both the comparisons data on impulsivity and depressive pathology were available, but no significant	

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

Randomised controlled trials

Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Shafti (2010)	**Study design:** 8 week, parallel groups, multicentre, double blind, randomised controlled trial. **Population:** Female inpatients meeting DSM criteria for BPD **Intervention:** olanzapine (started at 2.5mg daily, increased weekly at 2.5mg increments as required, to a maximum of 10mg by week 4). **Comparison:** haloperidol (started at 2.5mg daily, increased weekly at 2.5mg increments as required, to a maximum of 10mg by week 4). **Outcomes:** Primary outcome of a. Change in mean total score on the brief psychiatric rating scale	N=28 (14 participants in each group)	There was a significant positive response with both olanzapine and haloperidol at the end of the trial in comparison with the baseline for all outcomes, but no significant differences were observed between the treatment groups.	High (small sample size)

	(BPRS) Secondary outcomes of a. Change in mean score of the Clinical Global Impression Severity Scale (CGI-S) b. Change in mean score of the Buss-Durkee Hostility Inventory (BDHI)			
Zanarini (2011)	**Study design:** 12 week, placebo controlled, double blind, multicentre randomised controlled trial. **Population:** Male and female outpatients, 18-65 years of age and meeting at least 5 of 9 DSM-IV criteria for borderline personality disorder. People were excluded from the study if they DSM-IV thresholds for major depressive disorder, bipolar II disorder, PTSD, panic disorder, OCD. Participants were also excluded if actively suicidal or had a BMI of <17. Additionally subjects with a recent psychotic disorder, bipolar I disorder or recent substance dependence were excluded. **Intervention:** Two arms of this trial examined an active intervention. An olanzapine 2.5mg/d group and an olanzapine 5-10mg/d group. Treatment for both of these groups started at 2.5mg/d. For those allocated to the higher dose	N=451 (n=150 olanzapine 2.5mg/d, n=148 olanzapine 5-10mg/d, n=153 placebo)	**Primary outcome measure:** The olanzapine 5- to 10-mg/d group showed a statistically significantly greater mean baseline-to-endpoint decrease in ZAN-BPD total score relative to the placebo group (0.29; 95% CI, 0.06–0.52, p = 0.010). There was no significant difference between the olanzapine 2.5-mg/d group and the placebo group, although this measure approached significance (p = 0.062). The olanzapine 5- to 10-mg/d group showed significantly greater mean reductions compared with the placebo group on the anger, affective instability, and paranoid ideation or dissociation items of the ZAN-BPD, and a significantly greater mean reduction on the suicidal/self-mutilating behaviour item. Patients in the olanzapine 2.5-mg/d group had significantly greater reductions compared with the placebo group on 2 individual ZAN-BPD item scores (identity disturbance and suicidal/self-mutilating behaviour). **Secondary outcome measures:** The olanzapine 5- to 10-mg/d group - and also olanzapine 2.5 mg/day - showed significantly greater mean reductions compared with the placebo group on OAS-M irritability score, OAS-M suicidality	Low (likely)

	group, dosage was adjusted to 5mg/d after 1 week, and increased to 10mg/d in week 2 if clinically indicated. **Comparison:** Placebo **Outcome:** Primary outcome of : a. Mean change in the Zanarini Rating Scale for Borderline Personality Disorder (ZAN-BPD). Secondary outcomes of: a. The Montgomery-Asberg Depression Rating Scale (MADRS) b. the Overt Aggression Scale-Modified (OAS-M) c. Global Assessment of Functioning (GAF). d. The Symptom Checklist-90-Revised (SCL-90-R) e. The Sheehan Disability Scale		score, and Sheehan family life score. In addition, olanzapine 2.5 mg/d group showed improvements on Sheehan social life score compared to placebo, whereas olanzapine 5- to 10-mg/day showed significant improvements on the Sheehan work/school score and the SCL-90-R score. No significant differences for each dose compared with placebo were observed for current GAF score, or MADRS total score. **Adverse events:** Among treatment-emergent adverse events reported with a frequency ≥ 5% in any treatment group, somnolence, fatigue, increased appetite, and weight increase were reported significantly more frequently in the olanzapine 5- to 10-mg/d group compared with the placebo group. Somnolence, increased appetite, and weight increase were reported significantly more frequently, and nasopharyngitis significantly less frequently, in the olanzapine 2.5-mg/d group compared with the placebo group. The incidence of serious adverse events was 3.4% in the olanzapine 5- to 10-mg/d group, 0.7% in the olanzapine 2.5-mg/d group, and 5.9% in the placebo group. Mean baseline-to-endpoint change in weight was significantly different in the olanzapine groups versus the placebo group (olanzapine 2.5 mg/d: 2.09 ± 2.93 kg and olanzapine 5–10 mg/d: 3.17 ± 3.28 kg versus placebo: 0.02 ± 2.47 kg; both P values < .001). No significant differences were observed between treatment	

			groups in the incidence of treatment-emergent abnormal fasting glucose or lipids at any time during treatment, on any of the electrocardiogram measures, or for changes in extrapyramidal symptoms. There were significant increases in prolactin and other laboratory values in the olanzapine group when compared to placebo.	

Risk of Bias

Systematic reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review Process	Quality assessment	Synthesis
Stoffers et al. 2010	☺	☺	☺	☺	☺

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Shafti et al. 2010	?	?	☺	☺	☺	☺
Zanarini et al. 2011	?	?	☺	☺	☺	☺

☺Low Risk ☹High Risk ? Unclear Risk

Search Details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	borderline AND antipsychotic	29	1
DARE	1. (borderline adj3 personalit*) IN DARE 41 2. MeSH DESCRIPTOR Borderline Personality Disorder EXPLODE ALL TREES 27 3. #1 OR #2	54	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Borderline Personality Disorder] explode all trees 242 #2 "borderline personality disorder" 411 #3 bpd 611 #4 #1 or #2 or #3 863 #5 MeSH descriptor: [Antipsychotic Agents] explode all trees 3778 #6 "neuroleptic drugs" 168 #7 "neuroleptic agents" 47 #8 "antipsychotic drugs" 675 #9 #5 or #6 or #7 or #8 4201 #10 #4 and #9 48 Central only	19	2
PsycINFO	1. PsycINFO; BORDERLINE PERSONALITY DISORDER/; 3977 results. 2. PsycINFO; BPD.ti,ab; 3661 results. 3. PsycINFO; "borderline personality disorder".ti,ab; 6005 results. 4. PsycINFO; 1 OR 2 OR 3; 7464 results. 5. PsycINFO; exp NEUROLEPTIC DRUGS/; 25083 results. 6. PsycINFO; antipsychotic*.ti,ab; 20570 results.	76	

	7. PsycINFO; 5 OR 6; 32078 results. 8. PsycINFO; 4 AND 7; 218 results. 9. PsycINFO; CLINICAL TRIALS/; 7503 results. 10. PsycINFO; random*.ti,ab; 128739 results. 11. PsycINFO; groups.ti,ab; 364600 results. 12. PsycINFO; (double adj3 blind).ti,ab; 17766 results. 13. PsycINFO; (single adj3 blind).ti,ab; 1393 results. 14. PsycINFO; EXPERIMENTAL DESIGN/; 9062 results. 15. PsycINFO; controlled.ti,ab; 80070 results. 16. PsycINFO; (clinical adj3 study).ti,ab; 7878 results. 17. PsycINFO; trial.ti,ab; 67795 results. 18. PsycINFO; "treatment outcome clinical trial".md; 26742 results. 19. PsycINFO; 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18; 564197 results. 20. PsycINFO; 8 AND 19; 109 results. 21. PsycINFO; BIPOLAR DISORDER/; 19108 results. 22. PsycINFO; 20 not 21; 76 results.		
Embase	9. EMBASE; BORDERLINE PERSONALITY DISORDER/; 8792 results. 10. EMBASE; BPD.ti,ab; 7271 results. 11. EMBASE; "borderline personality disorder".ti,ab; 4776 results. 12. EMBASE; 9 OR 10 OR 11; 14295 results. 13. EMBASE; exp NEUROLEPTIC DRUGS/; 0 results. 14. EMBASE; antipsychotic*.ti,ab; 37097 results. 15. EMBASE; 13 OR 14; 37097 results. 16. EMBASE; 12 AND 15; 274 results. 17. EMBASE; exp ATYPICAL ANTIPSYCHOTIC AGENT/; 70941 results. 18. EMBASE; 15 OR 17; 85349 results. 19. EMBASE; exp BIPOLAR DISORDER/; 38373 results. 20. EMBASE; 12 NOT 19; 12815 results. 21. EMBASE; 18 AND 20; 429 results.	82	

	22. EMBASE; random*.ti,ab; 861227 results. 23. EMBASE; factorial*.ti,ab; 22463 results. 24. EMBASE; (crossover* OR cross-over*).ti,ab; 67591 results. 25. EMBASE; placebo*.ti,ab; 194687 results. 26. EMBASE; (doubl* ADJ blind*).ti,ab; 138881 results. 27. EMBASE; (singl* ADJ blind*).ti,ab; 14034 results. 28. EMBASE; assign*.ti,ab; 233074 results. 29. EMBASE; allocat*.ti,ab; 81424 results. 30. EMBASE; volunteer*.ti,ab; 172583 results. 31. EMBASE; CROSSOVER PROCEDURE/; 38578 results. 32. EMBASE; DOUBLE BLIND PROCEDURE/; 112709 results. 33. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 339988 results. 34. EMBASE; SINGLE BLIND PROCEDURE/; 18122 results. 35. EMBASE; 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34; 1377920 results. 36. EMBASE; 21 AND 35; 82 results.		
Medline	9. MEDLINE; BORDERLINE PERSONALITY DISORDER/; 4927 results. 10. MEDLINE; BPD.ti,ab; 5555 results. 11. MEDLINE; "borderline personality disorder".ti,ab; 3783 results. 12. MEDLINE; 9 OR 10 OR 11; 9586 results. 13. MEDLINE; exp NEUROLEPTIC DRUGS/; 120369 results. 14. MEDLINE; antipsychotic*.ti,ab; 26288 results. 15. MEDLINE; 13 OR 14; 128026 results. 16. MEDLINE; 12 AND 15; 349 results. 17. MEDLINE; ANTIPSYCHOTIC AGENTS/; 41225 results. 18. MEDLINE; 15 OR 17; 128026 results. 19. MEDLINE; BIPOLAR DISORDER/; 30986 results. 20. MEDLINE; 12 NOT 19; 8855 results. 21. MEDLINE; 18 AND 20; 254 results. 22. MEDLINE; "randomized controlled trial".pt; 371683 results.	203	

	23. MEDLINE; "controlled clinical trial".pt; 88214 results. 24. MEDLINE; randomized.ab; 291592 results. 25. MEDLINE; placebo.ab; 153170 results. 26. MEDLINE; "drug therapy".fs; 1690846 results. 27. MEDLINE; randomly.ab; 211415 results. 28. MEDLINE; trial.ab; 302627 results. 29. MEDLINE; groups.ab; 1346693 results. 30. MEDLINE; 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29; 3319957 results. 31. MEDLINE; 21 AND 30; 203 results.		
Summary	**NA**	**NA**	

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