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Novel Antipsychotics for Patients with Bipolar Disorder: A Systematic Review

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EXECUTIVE SUMMARY

Objectives: The purpose of this assessment is to assess the efficacy of the novel antipsychotic drugs (olanzapine, risperidone, quetiapine and clozapine) both as monotherapy and as add-on therapy for acute and maintenance treatment of bipolar disorder.

Methods: A systematic review was performed of clinical trials in which a novel antipsychotic drug was compared prospectively with placebo or with another agent for treatment of patients with bipolar disorder. A quality assessment of the studies was carried out.

Results: Of the 58 potentially relevant studies identified, eight met the inclusion criteria. In four studies, novel antipsychotic drugs were used as monotherapy for the acute treatment of mania. The other four studies considered novel antipsychotics as add-on therapy to regular treatment. Improvement in primary clinical outcome was measured through use of the Young Mania Rating Scale (YMRS). Available evidence suggests the novel antipsychotic olanzapine improves the treatment of acute mania in patients with bipolar disorder, as compared to placebo. No clear advantage is seen in a small trial (n=30) where olanzapine was compared with lithium. Information related to the efficacy of other novel antipsychotics as monotherapy or add-on therapy for the treatment of acute mania is limited and is not transparent. Studies show no significant difference between novel antipsychotics and traditional agents in the incidence of extrapyramidal side effects. Results of long-term therapy were not available.

Conclusions: Too little information is currently available to draw any meaningful conclusions concerning the use of novel antipsychotics in the treatment of bipolar disorder. Given the high cost of these agents, and the lack of conclusive evidence concerning their benefit over traditional therapies, a cautious approach is warranted when considering their use. This is a rapidly changing field and other trials with new information will soon be completed.
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1. INTRODUCTION

1.1 Clinical Background

Bipolar disorder, also known as manic-depressive disease, is a chronic progressive illness, which produces significant morbidity and mortality.1 If untreated, a manic episode generally lasts from one to three months. The condition is almost invariably associated with substantial negative interpersonal and social consequences.1 In the manic state, a patient may behave violently, and in the depressed state, death from suicide or from physical breakdown may occur.1,2

According to the Diagnostic and Statistical Manual on Mental Disorder, Fourth edition (DSM-IV), bipolar mood disorder is primarily of two types.2 An individual who has experienced one or more manic or mixed episodes (alternating symptoms of manic episodes and major depressive episodes) is diagnosed as having bipolar I disorder. Mania is defined as a distinct period of an abnormally elevated, expansive, or irritable mood lasting at least one week, with such symptoms as grandiosity, decreased need for sleep, racing thoughts, or excessive involvement in activities that have a high potential for painful consequences.3 An individual who has experienced one or more episodes of both hypomania and depression (without a history of manic or mixed episodes) is diagnosed as having bipolar II disorder.2 Hypomanic episodes are characterized as states of elevated mood, which are less severe than mania and which are not severe enough to impair functioning, complicate a medical condition, or result in psychotic features.

Sixty to 70% of manic or hypomanic episodes occur either immediately before or after a major depressive episode.2 Patients tend to return to normal function between episodes. Rapid cycling bipolar mood disorder is considered a specifier of longitudinal course rather than a specific mood disorder subtype in DSM-IV.4 In rapid-cycling bipolar mood disorder, a person has at least four episodes per year, as a combination of manic, hypomanic, mixed, and/or depressive episodes.

1.2 Epidemiology

An international, epidemiological study involving 38,000 community subjects from ten countries including Canada, reported that the lifetime rates of bipolar disorder are consistent across countries (0.3/100 to 1.5/100).5 According to the study, the incidence of bipolar disorder in Canada is 0.6 per hundred. The average age at the first onset is 20 years. Patients presenting with their first episode after 40 years of age generally have a causative medical condition rather than bipolar disorder. The male:female ratio of prevalence of this disease in Canada is 0.7. Females tend to experience more depressive episodes while males experience more manic episodes. Rapid cycling bipolar disorder tends to be seen more often in females than in males.2 Family history and cyclothymic disorder (episodes of milder hypomania and depression) are risk factors for the development of both bipolar I and II disorders.

1.3 Treatments

Treating bipolar disorder is a challenging clinical task. Details of the pharmacological treatment of bipolar disorder are available in recently published consensus guidelines.6 Mood stabilizers
including lithium, valproate and carbamazepine are primary agents used for the treatment of acute episodes and in the prevention of future episodes. None of the currently available mood-stabilizing agents uniformly lead to complete remission. For example, pooled data from four placebo controlled trials of lithium revealed a response rate of 78 percent. Hence, most clinicians use adjunctive medications, such as antidepressant and anti-psychotic agents, to treat “breakthrough” depressive or manic symptoms and/or to enhance overall mood stabilization.

Antipsychotics are commonly used for the treatment of acute mania to provide rapid control of psychopathology, particularly for very hyperactive or disturbed psychotic patients. Classic (typical) antipsychotic drugs produce a more rapid response than lithium, which may require up to ten days for a therapeutic effect. Lithium may be administered concomitantly or added to an antipsychotic regimen after an initial therapeutic response. Despite the lack of evidence for antipsychotic efficacy in maintenance treatment, recent data show that manic inpatients treated with antipsychotics for acute mania usually are not tapered off their antipsychotics after the acute manic episode. Different studies have found that these bipolar patients remained on antipsychotics for long periods of time.

There are well-established risks with the long-term use of typical antipsychotic agents including a significant risk of extrapyramidal side effects (EPS) [akinesia (slowness of voluntary movement), rigidity and tremor] and tardive dyskinesia (TD) (involuntary movements). Typical antipsychotics include all the agents introduced before clozapine. Chlorpromazine was the first typical antipsychotic.

All typical antipsychotics introduced after chlorpromazine provided no additional advantage with respect to efficacy, but instead offered a different adverse-effect profile and dosage form. Novel antipsychotics were developed in response to problems with typical agents. Clozapine was the first novel antipsychotic introduced. This drug caused a serious adverse effect, agranulocytosis, and is not commonly used. A number of new agents in this class have recently been introduced which do not cause agranulocytosis. These agents include risperidone, olanzapine and quetiapine. Pharmacologically, novel antipsychotics differ from typical antipsychotics in their “limbic specific” dopamine type 2 (D_2) receptor binding and high ratio of serotonin type-2 (5-HT_2)-receptor binding to D_2-receptor binding. This high 5-HT_2 to D_2 ratio has the advantage of decreasing EPS risk by enhancing dopaminergic transmission in the striatum.

Although the exact clinical definition of novel antipsychotics has not been provided, the following criteria are discussed in most definitions: a lower risk of EPS or tardive dyskinesia, improved cognitive functioning, antipsychotic activity in refractory patients and little effect on serum prolactin levels. The novel antipsychotics olanzapine, clozapine and risperidone may be associated with endocrine side effects such as weight gain and hypertriglyceridemia, whereas typical antipsychotics have less risk of causing weight gain compared to novel antipsychotics.

In Canada, clozapine, olanzapine, risperidone and quetiapine are the currently available novel antipsychotics. None are approved in Canada for the treatment of bipolar disorder as of May, 2001. Recently, olanzapine received approval for the treatment of mania from the Food and Drug Administration (FDA) in the US.
The results of the literature to date concerning the use of novel antipsychotics for bipolar disorder are not consistent. Two pivotal studies report that olanzapine is more effective than placebo as mono-therapy for mania.\textsuperscript{17,18} Literature supporting the use of risperidone and quetiapine for the treatment of bipolar disorder is also available.\textsuperscript{19-21} There are reports in the literature that do not support the efficacy of novel antipsychotics in bipolar disorder.\textsuperscript{22,23} These reports indicate that the novel antipsychotic risperidone, may actually exacerbate mania. However, according to recently published guidelines, novel antipsychotics can play a major role in the acute and prophylactic treatment of bipolar disorder.\textsuperscript{6}

In view of the disabling nature of bipolar disorder, it is important to examine the evidence of randomized trials reporting on the use of novel antipsychotics for the treatment of bipolar disorder.
2. OBJECTIVES

To critically examine, using best evidence synthesis methodology:

1. the evidence for the use of novel antipsychotics as monotherapy in both acute and maintenance treatment of bipolar disorder;
2. the evidence for the use of novel antipsychotics as adjunctive therapy in both acute and maintenance treatment of bipolar disorder; and
3. the evidence comparing the use of novel antipsychotics to classic antipsychotics (typical) and comparing one novel antipsychotic to another novel antipsychotic, in the acute and/or maintenance treatment of bipolar disorder.
3. METHODS

3.1 Criteria for considering studies for this review

3.1.1 Types of studies
All published and unpublished prospective randomized trials, both parallel and cross-over design, were included. Studies published as abstracts were also included.

3.1.2 Types of participants
Males and females of all ages with a diagnosis of bipolar mood disorder by any criteria, with all subtypes of bipolar mood disorder (rapid cycling, type I and II and other) were included. In trials that involve heterogeneous groups of subjects, in particular schizoaffective disorder and recurrent unipolar depression, the data were separated into diagnostic groups. Where such separation was impossible, the studies were included and detailed information about the groups was provided.

3.1.3 Types of intervention
Trials were included if they compared any of the novel antipsychotic drugs with placebo, classical antipsychotics, or other mood stabilizing agents such as lithium, valproate and carbamazepine. Trials in which one novel antipsychotic was compared with another novel antipsychotic and trials that considered a novel antipsychotic in combination with other drugs, were also included.

3.1.4 Types of outcome measures
The outcomes of interest were:

A. Acute phase treatment:
1. Clinical efficacy defined as an improvement in both manic and depressive episodes.
2. Total dropouts from the trial.
3. The number of patients who withdrew from the trial due to noncompliance.
4. The number of patients who withdrew from the trial due to side effects.
5. Any adverse effect(s), such as EPS, during the trials.

B. Maintenance treatment phase:
1. Relapse (however defined, including readmission to hospital).
2. Time to relapse.
3. Symptoms of mania or depression during follow-up, however measured.
4. Total dropouts from the trial.
5. Any adverse effect(s) experienced during the trials.
3.2 Literature search

Published literature was obtained by searching a number of databases (see Appendix 1). On the DIALOG® system, MEDLINE®®, EMBASE®®, Toxline® and PsycINFO® were searched, resulting in 235 unique records. Retrieval was limited to the publication years 1985-2000. There were no language restrictions. Database alerts/updates were established on Adis LMS Drug Alerts, Adis Newsletters, Current Contents Search®, EMBASE® Alert, MEDLINE®, Pharmaceutical News Index (PNI®), PsyINFO®, and Toxline®. The Cochrane Library on CD-ROM was searched and updated to Issue 2, 2001. Web sites of health technology assessment and near technology assessment agencies were also searched, as were specialized databases, such as the University of York NHS Centre for Reviews and Dissemination. The Google™ search engine was used to search for a variety of information on the Internet. These searches were supplemented by hand searching of selected journals and documents in the CCOHTA library collection and the bibliographies of selected papers. In addition, manufacturers of the different novel antipsychotics were contacted for information regarding unpublished studies.

3.3 Method of the review

3.3.1 Selection of potentially relevant studies

A single reviewer (VS) reviewed citations and discarded irrelevant ones, based on the title of the publication and its abstract, and retained those that were considered potentially relevant. Case reports, review articles and studies unrelated to the use of novel antipsychotics in bipolar disorder were discarded at this stage.

3.3.2 Selection of relevant studies

Potentially relevant studies were acquired from library sources. Two reviewers (VS and LM) independently made the final selection of the relevant studies to be included in the review. Disagreement regarding inclusion of any study was resolved by discussion. A third reviewer (VF) was available to adjudicate any persisting differences.

3.3.3 Assessment of quality

The quality of the included studies was assessed using the Jadad scale, which includes appropriateness of randomization and double blinding, and a description of withdrawal and dropouts. Information about allocation concealment to the intervention group was also recorded (appendix II). Two reviewers assessed the quality of the studies independently.

3.3.4 Data extraction

Two reviewers independently extracted data concerning participant characteristics, intervention details and outcome measures from the included studies (appendix III).
3.3.5 Statistical analysis

One reviewer entered data into Cochrane Review Manager. For binary efficacy outcomes, a pooled odds ratio (with 95% confidence intervals) was calculated using a fixed effects model. Tests of heterogeneity were done. For continuously distributed outcomes, the weighted mean differences were calculated. Intention-to-treat data were used when available. Where this was not possible, end-point data for persons completing trials were used. Qualitative data are presented descriptively.
4. RESULTS

After reviewing the titles and abstracts of the studies obtained from different data sources, 58 potentially relevant studies were identified by a single reviewer (VS). Of these, eight randomized controlled trials (RCT) were identified for potential inclusion in the systematic review by two reviewers (VS and LM) and the remaining studies were excluded (Figure 1, Table 1 and Appendix IV). There was no disagreement between the two reviewers.

The quality assessment of these studies by the Jadad scale showed that four studies were of moderate quality (quality scores 3 to 4) and four were of low quality (0 to 2). Allocation concealment was not clearly described in any of the studies. The degree of agreement between the two evaluators in quality assessment was 100 percent.

Table 1 provides details about the included studies. Olanzapine, risperidone and clozapine were the novel antipsychotics assessed in these studies. No studies considering the use of quetiapine were identified. Four studies were from the United States, two from South Africa, one from Italy and one from Canada. Seven were funded by industry and the funding source was not indicated for the remaining one. Information on patient withdrawal due to non-compliance was not clearly described in any of the studies.

No studies comparing one novel antipsychotic to another were identified; therefore Objective 3 could not be addressed. Due to the small number of studies included in this review and the few outcomes available for pooling across the studies, statistical heterogeneity was not demonstrated. Details of the different scales used for measuring different clinical outcomes are available in appendix V.

4.1 Novel antipsychotic drugs for acute treatment of mania

4.1.1 Novel antipsychotics as mono-therapy in acute treatment

Four studies were related to the use of novel antipsychotics as mono-therapy for the acute treatment of mania in patients with bipolar disorder.

4.1.1.1 Novel antipsychotics vs. placebo: Olanzapine is the only novel antipsychotic compared with placebo; and this was done in two studies by the same group. Pooled analysis of the data from these two studies showed that olanzapine was more effective than placebo when various outcome measures were considered (Fig 2). For non-responders as an outcome, the Peto Odds Ratio (OR) was 0.37 [with 95% confidence intervals (CI) 0.22; 0.61]. [A non-responder is defined as any patient achieving less than a 50% decrease in total score on the Young Mania Rating Scale (YMRS) from baseline to endpoint.] The number of dropouts in the placebo group was significantly higher than that in the olanzapine group (Peto OR: 0.37, 95%CI 0.22; 0.60). For outcomes measures with continuous data [e.g. YMRS scores, Positive and Negative Symptoms Scale (PNSS) scores, Clinical Global Impression (CGI) scale score and the 21-item Hamilton Depression Rating Scale (21-HDRS) scores], baseline to endpoint score differences in the olanzapine and the placebo groups were compared. A significant improvement (decrease) in YMRS scores was observed between olanzapine and placebo groups [weighted mean difference
Significant improvements in PNSS scores (WMD: -9.94, 95%CI -14.72; -5.17) and CGI scale scores (WMD: -0.58, 95%CI -0.93; -0.24) were also observed.

Quality of life was assessed in one study with the 36-item Short-Form Health Survey (SF-36) questionnaire and no difference was observed between the olanzapine and placebo groups. No significant difference was observed between olanzapine and placebo in relation to EPS as measured by the Simpson-Angus Rating Scale (SARS) scores (WMD: -0.32, 95%CI -0.74; 0.09) and Barnes Akthasia scale (BAS) scores (WMD: -0.13, 95%CI -0.32; 0.06). Olanzapine also caused a significant weight gain compared to placebo treatment (WMD: 1.91 kg, 95% CI 1.29 kg; 2.53 kg).

4.1.1.2 Novel antipsychotics versus other agents: One study compared olanzapine to lithium and one compared risperidone, haloperidol and lithium. The same research group did both the studies. The WMD for different outcome measures were not calculated because the standard deviation values around the differences between baseline and end point scores for different outcomes were neither available in the study report nor from the study author. No study comparing one novel antipsychotic with another novel antipsychotic was available.

Olanzapine and lithium were equally efficacious for different outcome measures. The percent reductions (improvements) from baseline for different scale scores for olanzapine versus the lithium group were: 67% versus 58% for YMRS, 47% versus 40% for Brief Psychiatry Rating Scale (BPRS), 51% versus 39% for the CGI-severity and 45% versus 36% for the CGI-improvement scale. On the CGI-severity scale score, olanzapine showed a significant advantage over lithium (P=0.018). The clinical significance of this difference is not explained in the study. Neither olanzapine nor lithium produced EPS, as indicated by no significant difference in baseline and end point scores on the SARS and the Barnes Akthasia Scale. The numbers of dropouts from the olanzapine and lithium groups were one and three, respectively.

In the study comparing risperidone, lithium, and haloperidol, all the drugs were equally efficacious in improving different efficacy outcome measures. The percent reduction from baseline to endpoint for different scale scores for risperidone, haloperidol, lithium were 57%, 59%, and 45% for YMRS, 63%, 68%, and 48% for BPRS and 52%, 56%, and 35% for CGI scale. The percent improvement in Global Assessment of Functioning Scale (GAF) scores was 87%, 54% and 67% for risperidone, haloperidol and lithium, respectively. No significance differences were observed among the three groups in any of the scale scores.

Risperidone and haloperidol were more prone to producing EPS as compared to lithium. In the same study, SARS scores were increased from 1.33 to 3.93 (195% increase) and 0.46 to 2.66 (478% increase) in the risperidone and haloperidol groups, respectively. In the lithium group, SARS scores decreased from 0.66 to 0.40 (39% decrease). The number of dropouts in the risperidone, haloperidol and lithium groups was two, three and one, respectively.
4.1.2 Novel antipsychotic drugs as add-on therapy in acute treatment

Clozapine or chlorpromazine as add-on therapy with lithium caused a significant reduction (improvement) in YMRS scores after three weeks of treatment in bipolar patients with acute manic episodes in one study.\(^{26}\) The percent reductions from the baseline to the end point in YMRS scores for clozapine and chlorpromazine were 90% and 79%, respectively. The number of patients showing EPS in clozapine and chlorpromazine groups was 1 out of 15 and 7 out of 15, respectively.

Two three-week studies comparing risperidone with placebo and/or haloperidol as add-on therapy to regular treatment were available as abstracts.\(^{27,28}\) In these studies the data for different clinical outcome measures were extracted from the figures. Data could not be pooled to calculate WMD for various outcome measures because standard deviation values around differences between baseline and end point scores were not available in the abstracts.

In the study comparing risperidone and placebo as add-on therapy to regular treatment (either lithium, valproate or carbamazepine) the changes from baseline to end point YMRS scores were not significantly different between the risperidone and placebo groups (risperidone -14.5 versus placebo -10.5; \(p=0.098\)).\(^{28}\) The number of responders (patients achieving \$50\% reduction in YMRS from the baseline) was significantly higher in the risperidone group compared to the placebo group (58.8\% versus 41.7\%; \(p<0.05\)). Although it is not clear from the publication whether these percentages were calculated as a percentage of the total patients randomized in the study or as a percentage of the number of patients completing the study, the manufacturer informed us it was an intention-to-treat analyses.

Statistically significant differences between risperidone and placebo, in favor of risperidone, were observed for improvements from baseline to endpoint on the CGI scale (risperidone 60\% versus placebo 42\%; \(p<0.03\); change in scores in absolute number is not available) and BPRS (risperidone -12.5 versus -10.5; \(p<0.01\)). The values of baseline scores for any of the outcome measures were not available in the study. The percentage of events related to EPS occurring in risperidone and placebo groups were 21.3\% and 8\%, respectively. The number of dropouts in the placebo group was higher than that in the risperidone group (risperidone 29 versus placebo 41).

In the second study comparing risperidone, haloperidol and placebo as add-on therapy to a mood stabilizer (either lithium or valproate), the total changes from baseline to endpoint in YMRS scores in different groups were -14.3, -13.3 and -8.2, respectively.\(^{27}\) The number of responders in different groups was 57\%, 58\% and 38\%, respectively. No significant difference was noted among risperidone, haloperidol and placebo in changes from baseline to endpoint in BPRS scores and HDRS scores. The total number of subjects with at least one adverse event in the risperidone, haloperidol and placebo groups were 42, 48 and 43, respectively. The number of patients with EPS in the different groups was seven, 15 and two, respectively.
4.2 Novel antipsychotics for maintenance treatment of bipolar disorder

In one study, clozapine as an add-on (for one year) to regular therapy was compared with regular therapy alone in bipolar I disorder or schizoaffective disorder patients with a history of mania. These patients had a history of treatment resistance or intolerance to regular therapy. Patients with an onset of illness after the age of 40 were excluded on the basis of evidence indicating that late-onset bipolar disorder often results from secondary causes. At baseline and every two weeks for three months thereafter, patients were administered the BPRS, the CGI scale, the Bech-Rafaelsen Mania scale, the HDRS, the Scale for the Assessment of Positive Symptoms, the Scale for the Assessment of Negative Symptoms and the Abnormal Involuntary Movement scale.

The author reported that clozapine add-on therapy produced a significant improvement compared to regular therapy in the mean rate of change in BPRS scale scores, Bech-Rafaelsen Mania scale scores, CGI scale scores, the Scale for the Assessment of Positive Symptoms scores and the Scale for the Assessment of Negative Symptoms scores. A pattern mixture random regression-model was used to calculate and compare the rate of change in the two groups. This model takes into account the effect of dropouts on the comparison. In the results, end point scores for different outcome measures were not available. Dropouts were greater in the regular therapy treatment group (n=9) than the clozapine group (n=3).
5. DISCUSSION

To our knowledge this is the first systematic review of RCT’s examining the use of novel antipsychotics in bipolar disorder. A number of review articles have appeared recently on this subject.\textsuperscript{15,29-34} In these review articles, in addition to RCTs, case reports, case series, or open trials were included. The majority of these studies describe a benefit of the use of novel antipsychotics over typical antipsychotics.

The number of case reports, case series, or open trials available in the literature which report on the use of novel antipsychotic drugs in bipolar disorder is about seven times greater than the number of RCTs. Conclusions based on case reports and case series can be misleading because of the questionable validity of such reports. Case reports as a study-design are used for hypothesis generating not for hypothesis testing.\textsuperscript{35}

Uncontrolled studies are unable to offer firm conclusions because of the self limiting nature of mania;\textsuperscript{35,36} untreated mania tends to resolve within one to three months.\textsuperscript{30} Placebo controlled trials are seen as the only scientifically sound way to test the efficacy of most psychiatric drugs due to a high placebo response rate.\textsuperscript{37} According to the FDA, without a placebo-controlled trial, it is hard to prove the efficacy of a psychiatric drug.\textsuperscript{37} In a recent analysis of different randomized controlled studies on acute bipolar mania, the mean (\textsuperscript{\textdagger}) percentage of placebo responders was 23\% (\textsuperscript{\textdagger} 11\%; range 11-43%) compared with 40\% (\textsuperscript{\textdagger} 24 \%; range 8-65\%) for drug responders.\textsuperscript{38}

In our study, olanzapine was found to be more effective than placebo in a battery of clinical assessment measures for the treatment of acute attacks of mania in patients with bipolar disorder. The effect size varies for different clinical assessment measures. When the outcome “number of responders” was considered, olanzapine was almost three times more effective than placebo. (A responder is defined as any patient achieving more than a 50\% decrease in total score on the YMRS from baseline and endpoint.) In the continuous clinical assessment measures including YMRS scores, CGI scale scores and PNSS scores, olanzapine showed a significant advantage over placebo. YMRS is a more mania-specific scale.\textsuperscript{39} It covers the assessment of 11 aspects of mania, including elevated mood, motor activity, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive-aggressive behavior, appearance and insight. Each aspect has five grades of severity explicitly defined. On the YMRS, olanzapine produced, approximately, a six point greater improvement when compared to placebo (appendix V).

A limited use of benzodiazepines (lorazepam) was allowed in the four studies examined in this analysis. Lorazepam is effective as an adjunctive treatment of manic agitation in bipolar patients and may have contributed to the high placebo response, as well as the response attributed to olanzapine.\textsuperscript{40}

One study comparing olanzapine and placebo for the treatment of acute mania evaluated an outcome related to patient perception of improvement in health-related quality of life (HRQoL) using SF-36.\textsuperscript{17} No overall difference was observed between olanzapine and placebo. SF-36 has eight subscales measuring physical functioning, role functioning (work and other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social
functioning, and mental health. The validity of the quality of life assessment in patients with bipolar mood disorder can be questioned due to the cyclical nature of the illness, and the very fact that bipolar patients often enjoy the euphoria and other positive feelings associated with mania.\textsuperscript{41}

Olanzapine treatment caused a statistically significant weight gain compared to placebo. Weight gain liability of novel antipsychotic is greater than the typical antipsychotics.\textsuperscript{16} Olanzapine did not produce any significant EPS compared to placebo. About twice as many patients taking placebo discontinued compared to those taking olanzapine.

The applicability of the results of studies comparing:
- novel antipsychotics with other agents in acute treatment of mania;
- novel antipsychotics as add-on therapy in acute treatment of mania; and
- novel antipsychotics for maintenance treatment of bipolar disorder;

is limited in this review, because no overall analysis was possible. This can be attributed to two factors: (1) only a small number of RCTs were available which met the inclusion criteria for each of the three situations mentioned above and (2) it was not possible to obtain necessary data from the study authors. In addition, no studies comparing one atypical antipsychotic to another were identified.

The sample sizes in the studies that did meet the inclusion criteria were small (Table 1). A single study with small sample size and subjectively measured outcomes is prone to produce false positive and false negative results. The absence of a placebo arm in the studies comparing novel antipsychotic drugs and other agents for the acute treatment of mania may be problematic. According to the FDA, it is common in psychiatric drug trials to observe that 30\% to 50\% of patients improve in the placebo arm.\textsuperscript{37} Due to this high placebo effect, even already-approved drugs regularly fail to outperform the placebo in later trials.
6. CONCLUSIONS

At this stage the evidence suggests that the novel antipsychotic olanzapine improves the treatment of acute mania in patients with bipolar disorder, as compared to placebo. No clear advantage is seen in trials where olanzapine was compared with lithium. Information related to the efficacy of other novel antipsychotics as monotherapy or as add-on therapy for the treatment of acute mania is limited and is not transparent.

Too little information is available to draw any meaningful conclusion concerning the use of novel antipsychotics in the chronic treatment of bipolar disorder.

To conclude, the small quantity of information on the benefits of novel antipsychotics over traditional therapies in patients with bipolar disorders makes any conclusion and cost/benefit analysis premature. A cautious approach is warranted when considering their use. This is a rapidly changing field and other trials with new information will soon be completed. Bipolar disorder is a disabling disease, which is difficult to manage. As clinicians and patients strive to find acceptable and useful therapies, they must carefully weigh the evidence concerning the benefits and side effects before adopting a seemingly helpful treatment.
7. REFERENCES


Figure 1: Progress through the stages of meta-analysis including selection of potentially relevant studies, included and excluded

Potentially relevant studies identified and screened for retrieval [N=58]

\[\downarrow\]

Studies excluded (N=40)
Case series and case reports=29, Chart reviews=6, Patients with bipolar affective disorder not included=3, Studies not related to atypical antipsychotics=2

\[\downarrow\]

Full studies retrieved for more detailed evaluation (n=18)

\[\downarrow\]

Studies excluded for broad reasons (n=10)
(Abstracts available as full studies=2, Abstract related to the subgroup analysis or part of the full study= 6, Number of patients in control and treatment group are not available separately=1, No control group in the study=1.

\[\downarrow\]

Potentially appropriate studies for inclusion in systematic review (n=8)

\[\downarrow\]

Studies included in the systematic review (n=8)
Figure 2: Meta-analysis of the data of different clinical outcome measure of randomized trials comparing olanzapine and placebo in bipolar I disorder with acute mania.

<table>
<thead>
<tr>
<th>Comparison or Outcome</th>
<th>Peto Odds Ratio (95% CI)</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics vs placebo</td>
<td></td>
<td></td>
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<tr>
<td>Difference in YMRS-scores</td>
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<tr>
<td>Difference in positive/negative syndrome score</td>
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<tr>
<td>Comparison of 21-HDRS scores</td>
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<tr>
<td>CGI scores</td>
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<td>Non-responder in olanzapine and control group</td>
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<td>Dropout in olanzapine and control group</td>
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<td>Simpson-Angus rating scale scores changes</td>
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<td>Comparison Barnes Akthesia scale scores</td>
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<tr>
<td>Weight gain due to olanzapine treatment</td>
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</table>

![Graph showing comparison results]
TABLE 1: Atypical antipsychotics for bipolar disorder: characteristics of included studies

<table>
<thead>
<tr>
<th>Study &amp; Funding Source</th>
<th>Method</th>
<th>Quality Assessment Scores</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tohen et al, 1999&lt;sup&gt;17&lt;/sup&gt; Industry</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>139 patients with bipolar I disorder according to DSM-IV criteria, manic or mixed episodes of at least 2wks duration, YMRS scores: $20, patients hospitalized for at least 1 week</td>
<td>OLZ 10 mg /day (adjusted between 5-20 mg/day) or placebo for 3 wks</td>
<td>Primary outcome: changes in YMRS scale scores, other outcome measures HDRS scores, PNSS scores, CGI-BP scale scores and SF-36 for QoL. For EPS SARS scores, BAS scores and the abnormal in voluntary movement scale score</td>
<td>Lorazepam (up to 4 mg/day during 1&lt;sup&gt;st&lt;/sup&gt; week and then up to 2 mg/day) was allowed on as needed basis (PRN) during the trial</td>
</tr>
<tr>
<td>Tohen et al., 2000&lt;sup&gt;18&lt;/sup&gt; Industry</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>115 patients with bipolar I disorder according to DSM-IV criteria with manic or mixed episode with or without psychotic feature, YMRS scores $20, patients hospitalized for at least one week</td>
<td>OLZ 15 mg/day (adjusted between 5 to 20 mg/day) or placebo for 4 wks</td>
<td>Primary outcome: changes in YMRS scale scores, other outcome measures HDRS scores, PNSS scores, CGI-BP scale scores. For EPS SARS scores and BAS scores</td>
<td>Lorazepam PRN (up to 2 mg/day for 1&lt;sup&gt;st&lt;/sup&gt; 4 days then 1 mg/day for next 6 days) was allowed</td>
</tr>
<tr>
<td>Berk et al., 1999&lt;sup&gt;14&lt;/sup&gt; Industry</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>30 hospitalized patients with bipolar disorder according to DSM-IV criteria with acute manic episode</td>
<td>OLZ 10 mg/day or lithium 400 mg, BID for 4 wks</td>
<td>YMRS score, BPRS score, CGI scale score and GAF score. For EPS SARS score and BAS score</td>
<td>Lorazepam PRN allowed</td>
</tr>
<tr>
<td>Segal et al., 1998&lt;sup&gt;20&lt;/sup&gt; Industry</td>
<td>RCT, DB, parallel group study</td>
<td>2</td>
<td>45 hospitalized patients with bipolar disorder (according to DSM-IV criteria) with an acute manic episode</td>
<td>RIS 6 mg/day, HAL 10 mg/day, lithium 800 to 1200 mg / day for 4 weeks</td>
<td>YMRS scores, BPRS score, CGI scale score, and GAF score. For EPS SARS scores.</td>
<td>Lorazepam PRN allowed</td>
</tr>
<tr>
<td>Yatham, 2000&lt;sup&gt;28&lt;/sup&gt; * Industry</td>
<td>RCT, DB, parallel group study</td>
<td>3</td>
<td>150 hospitalized patients with bipolar manic or mixed episode (138 bipolar manic and 12 mixed episode)</td>
<td>RIS (mean modal dose 3.68 mg/day)+ regular treatment or placebo + regular treatment for 3 wks</td>
<td>YMRS scores, BPRS score, HDRS score and CGI scale scores</td>
<td>No information available</td>
</tr>
<tr>
<td>Sachs G 2001&lt;sup&gt;27&lt;/sup&gt; * Industry</td>
<td>RCT, DB, parallel group study</td>
<td>2</td>
<td>158 acutely manic bipolar inpatients receiving a mood stabilizer</td>
<td>RIS (2-6 mg/day), HAL (2-12 mg/day) and placebo with regular treatment for 3 wks</td>
<td>YMRS scores, BPRS score and HDRS scores, EPS scores</td>
<td>No information available</td>
</tr>
<tr>
<td>Barbini et al., 1997&lt;sup&gt;26&lt;/sup&gt; No information</td>
<td>RCT, open label, parallel group study</td>
<td>2</td>
<td>30 hospitalized bipolar disorder patients according to DSM-IV criteria with a manic episode</td>
<td>CLP (mean dose 166 mg/day) or CPZ (mean dose 310 mg/day) as an add-on therapy to lithium for 3 weeks</td>
<td>YMRS scores. For EPS SARS scores</td>
<td>No information available</td>
</tr>
<tr>
<td>Suppes et al., 1999&lt;sup&gt;21&lt;/sup&gt; Industry</td>
<td>RCT, open label, parallel group study</td>
<td>2</td>
<td>38 patients with history of mania by DSM-IV criteria, diagnosed with either schizoaffective disorder bipolar type, or bipolar I disorder.</td>
<td>Regular treatment or regular treatment +CLP (mean dose 355 mg/day) for one year</td>
<td>BPRS scores, CGI scale scores, Bech-Rafaelsen Mania scale scores, HDRS-24 score, SAPS, SANS. For EPS the Abnormal Involuntary Movement Scale</td>
<td>No information available</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; DB: double blind, OLZ: Olanzapine; RIS: Risperidone; CLP: Clozapine, CPZ: Chlorpromazine; HAL: Haloperidol, YMRS: Young-Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; PNSS: Positive and Negative Syndrome Scale; CGI-BP: Clinical Global Impression, bipolar version; QoL: Quality of Life; SF-36: Short form Health survey; EPS: Extrapyramidal Side effects; SARS: Simpson-Angus Rating Scale; BAS: Barnes Akathisia Scale; BPRS: Brief Psychiatry Rating Scale; GAF: Global Assessment Functioning Scale;

*Only available as abstract
## APPENDIX 1: Databases Searched and Strategies

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<tr>
<th>DATABASES</th>
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<th>KEYWORDS</th>
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<td>manic depressive psychosis!(l)dt <strong>OR</strong> (manic depressive psychosis! <strong>AND</strong> drug therapy! <strong>OR</strong> bipolar(w)depression/ti,ab <strong>OR</strong> manic(w)depressi?/ti,ab <strong>OR</strong> manic(w)disorder?/ti,ab <strong>OR</strong> manic(w)state?/ti,ab <strong>OR</strong> bipolar(w)affective(w)disorder?/ti,ab <strong>OR</strong> bipolar(w)mood(w)disorder?/ti,ab <strong>OR</strong> bipolar(w)I/ti,ab <strong>OR</strong> bipolar(w)II/ti,ab <strong>AND</strong> risperidone/de <strong>OR</strong> clozapine/de <strong>OR</strong> olanzapine/de <strong>OR</strong> quetiapine/de <strong>OR</strong> ziprasidone/de <strong>OR</strong> amisulpride/de <strong>OR</strong> risperidone/ti,ab <strong>OR</strong> clozapine/ti,ab <strong>OR</strong> Olanzapine/ti,ab <strong>OR</strong> Quetiapine/ti,ab <strong>OR</strong> ziprasidone/ti,ab <strong>OR</strong> amisulpride/ti,ab <strong>OR</strong> atypical(w)antipsycho?/ti,ab <strong>OR</strong> new(w)generation(w)antipsycho?/ti,ab <strong>OR</strong> second(w)generation(w)antipsycho?/ti,ab <strong>OR</strong> novel(w)antipsycho?/ti,ab <strong>OR</strong> atypical(w)neuroleptic?/ti,ab <strong>OR</strong> rn=111974-69-7 <strong>OR</strong> 111974-72-2 <strong>OR</strong> 5786-21-0 <strong>OR</strong> 106266-06-2 <strong>OR</strong> 132539-06-1 <strong>OR</strong> 146939-27-7 <strong>OR</strong> 138982-67-9 <strong>OR</strong> 71675-85-9 <strong>OR</strong> tn=seroquel <strong>OR</strong> clozaril <strong>OR</strong> leponex <strong>OR</strong> risperdal <strong>OR</strong> belivon <strong>OR</strong> rispolin <strong>OR</strong> zyprexa <strong>OR</strong> deniban <strong>OR</strong> solian <strong>OR</strong> sulamid <strong>AND</strong> dt=review <strong>OR</strong> short survey <strong>OR</strong> meta analysis <strong>OR</strong> multicenter study <strong>OR</strong> clinical study!/de <strong>OR</strong> controlled study!/de <strong>OR</strong> evidence based medicine!/de <strong>OR</strong> random?/ti,ab <strong>OR</strong> double(w)blind?/ti,ab <strong>OR</strong> double(w)dummy?/ti,ab <strong>OR</strong> placebo?/ti,ab <strong>OR</strong> meta(w)analy?/ti,ab <strong>OR</strong> metaanaly?/ti,ab <strong>OR</strong> quantitative?(w)review?/ti,ab <strong>OR</strong> quantitative(w)overview?/ti,ab <strong>OR</strong> systematic(w)review?/ti,ab <strong>OR</strong> systematic(w)overview?/ti,ab <strong>OR</strong> methodologic?(w)review?/ti,ab <strong>OR</strong> methodologic?(w)overview?/ti,ab <strong>OR</strong> collaborative(w)review?/ti,ab <strong>OR</strong> collaborative(w)overview?/ti,ab <strong>OR</strong> integrative(w)research(w)review?/ti,ab</td>
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21
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<td>Websites of health technology assessment and near health technology assessment agencies; other databases</td>
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<td>The Cochrane Database of Systematic Reviews = 13 complete reviews, 3 protocols; The Database of Abstracts of Reviews of Effectiveness = 2 reference; The Cochrane Controlled Trials Register = 52 references; Health Technology Assessment Database = 1 abstract by INAHTA and other healthcare technology assessment agencies; NHS Economic Evaluation Database = 2 references</td>
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<td>Same strategy and keywords, excluding clinical trial filter, as per DIALOG OneSearch®</td>
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</table>

Same keywords, excluding clinical trial filter, as per DIALOG OneSearch®
APPENDIX II

Study Quality

RM # ___________________________  Reviewer  _________________

Randomization: Total Points:  □ 0  □ 1  □ 2

A trial reporting that it is “randomized” is to receive one point. Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point. However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) a point is deducted.

Double-blind: Total Points:  □ 0  □ 1  □ 2

A trial reporting that is “double blind”, it is to receive one point. Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to receive an additional point. However, if the report describes the trial as double blind and uses an inappropriate method (e.g., comparison of tablets versus injection with no double dummy), a point is deducted.

Withdrawals and dropouts: Total Points:  □ 0  □ 1

A trial reporting the number and reason for withdrawals is to receive one point. If there is no statement, no point is given.

TOTAL Score  □ Low (0-2 pts)  □ Moderate (3-4 pts)  □ High (5 pts)

Allocation concealment  □ Adequate  □ Inadequate  □ Unclear

Adequate: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes, etc.

Inadequate: Alternation; reference to case record # or date of birth, etc.

Unclear: Allocation concealment approach is not reported or fits neither of the above categories.
## APPENDIX III

### EFFICACY STUDY RESULTS: ACUTE/MAINTENANCE

| Study No: |
| Reference: |

| Industry sponsorship: | Yes / No / no info |
| Are the patients randomly assigned to the treatment conditions: | Yes / No |
| Is the study double blinded: | Yes / No Parallel / Crossover |
| Is a criterion for diagnosis of bipolar depression provided: | Yes / No |

| Study arms |  |
| Dose & frequency |  |
| Duration of treatment |  |
| Pretreatment washout period |  |
| Other drugs allowed during the trial |  |

| Number of patients | Screened |  |
| Eligible |  |
| Randomized |  |
| Evaluable |  |
| Sex | M/F |  |
| Age (years) |  |
| Mean number of previous manic episodes |  |
| Mean number of previous depressive episodes |  |
| Mean duration of episode |  |

### Symptom resolution

<p>| Improvement in BPRS scores |  |
| Improvement in mania rating scale scores (MAS) |  |
| Improvement in global assessment of functioning scale scores (GAF) |  |
| Improvement in Clinical Global Impression scale (CGI) |  |
| Number of manic and depressive episodes |  |
| Total number of dropouts |  |
| Study Arm |  |
| Relapses |  |
| Time to relapse |  |</p>
<table>
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<td>Incidence of tardive dyskinesia</td>
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<td>Barnes Akathisia Scale scores</td>
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<td>Incidence of tardive dyskinesia and EPS</td>
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<td>Simpson-Angus Scale scores (EPS)</td>
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APPENDIX IV: List of the Excluded Studies

I. Case series or case reports


II. Chart reviews


III Patients with bipolar affective disorder were not included in the study


IV. Studies not related to atypical antipsychotics:


V. Abstracts related to the full study included in the analysis


VI. Information on number of patients in control and treatment group is not available

APPENDIX V: Different scales used for measuring clinical outcomes in patients with bipolar disorders.

**Young Mania Rating Scale (YMRS):** YMRS is a checklist of eleven items scale designed to measure the severity of manic symptoms and to gauge the effect of treatment on mania severity. Seven items (elevated mood, increased motor activity-energy, sexual interest, sleep, irritability, speech, language–thought disorder) are scored 0-4 and four items (content, disruptive-aggressive behavior, appearance, and insight) are scored 0-8. All the items have descriptors for every other increment.

**Bech-Rafaelsen Mania Scale (BRMS):** BRMS consists of eleven items including motor activity, verbal activity, flight of thoughts, voice/noise level, hostility/destructiveness, mood (feeling of well-being), self-esteem, contact, sleep, sexual interest and work. Each item is defined on a five-point scale (0= not present or habitual, 1 = mild, 2= moderate, 3 = marked, and 4 = severe or extreme). The range of the total score is 0 to 44.

**Clinical Global Impressions (CGI) Scale:** The CGI scale is a standardized assessment tool to estimate rate and severity of illness, change over time, and efficacy of medication. It is widely used in psychopharmacology trials as an outcome. The CGI scale consists of three global subscales: (i) Severity of illness subscale ranges from 1= not ill at all to 7= among the most extremely ill, (ii) Global improvement subscale goes from 1= very much improved to 7= very much worse and (iii) efficacy index in which the score ranges from 0 = marked improvement and no side effects to 4 = unchanged or worse and side effects outweigh therapeutic effects.

**Positive and Negative Syndrome Scale (PNSS):** The PNSS is designed to measure the severity of psychopathology in adult patients with schizophrenia, schizoaffective disorder, and other psychotic disorders and it emphasizes positive and negative symptom dimensions. This scale includes three scales and 30 items: 7 items make up the Positive scale (examples are delusions, conceptual disorganization, and hallucinatory behavior), 7 items make up the Negative scale (examples are blunted affect, emotional withdrawal, poor rapport, and passive/apathetic social withdrawal) and 16 items make up the general psychopathology scale (examples are somatic concerns, anxiety, guilt feeling, mannerisms and posturing, motor retardation, uncooperativeness, disorientation, poor impulse control, and preoccupation).

**Brief Psychiatric Rating Scale (BPRS):** BPRS is developed primarily to assess change in psychotic inpatients. It covers a broad range of areas including thought disturbances, emotional withdrawal and retardation, anxiety and depression, and hostility and suspiciousness. Its 18 items are rated on a seven-point item-specific Likert scale from 0 to 6, with the total score ranging from 0 to 108 (in some scoring systems, the lowest level for each item is 1, and the range is 18 to 126).

**Hamilton Rating Scale for Depression (HRSD):** HRDS is used to monitor the severity of major depression with a focus on somatic symptomatology including depressed mood, feelings of guilt, suicide tendency, insomnia, etc. It has two versions, one has 17 items and another has 24 items. The HRSD with 17 items is most commonly used. Items on HRSD are scored 0 to 2 or 0
to 4, with total scores on the 17-item version ranging from 0 to 50: a score of 7 or less may be considered normal; 8 to 13 mild; 14 to 18 moderate; 19 to 22 severe; and 23 and above very severe.

Rating Scale for Extrapyramidal Side Effects or Simpson-Angus Extrapyramidal Rating Scale: This scale is used to assess parkinsonian and related extrapyramidal side effects. It has ten items including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, akathisia, head dropping, glabella tap, tremor and salivation. Each item is rated on a fully anchored 5-point scale, with 0= the absence of the condition or normal and 4= the most extreme form of the condition.

Barnes Akathisia Rating Scale (BAS): This is a four item scale to measure drug-induced akathisia. Three items including objective akathisia, subjective awareness of restlessness, and subjective distress related to restlessness are rated on a 4-point scale (0-3). The fourth item, the global clinical assessment of akathisia, uses a 5-point scale (0-4).

Global Assessment of Functioning scale (GAF): GAF is a single rating scale for evaluating the overall functioning of a subject during a specified time period on a continuum from psychological or psychiatry sickness to health. The scale value ranges from 1, which represents the hypothetically sickest individual, to 100, the hypothetically healthiest. The scale is divided into ten equal intervals: 1 to 10, 11 to 20, and so on to 81 to 90 and 91 to 100. The defining characteristics of each ten-point interval comprises the scale.

36-Item Short Form Health Survey (SF-36): The SF-36 is one of the most commonly used measures of quality of life. The SF-36 was designed to understand the burden of chronic disease and the effect of treatments on general health status. It has eight subscales measuring physical functioning, role functioning (work or other activities) affected by both physical and emotional symptoms, pain, general health, vitality, social functioning, and mental health. These eight subscales may be collapsed into two domain scores reflecting physical and mental components of quality of life.