A Systematic Review of the Treatment of Borderline Personality Disorder using Fluoxetine and Olanzapine

By

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Abstract

BACKGROUND: Borderline personality disorder (BPD) is prevalent among the general population (2%). Treatment of BPD is with the use of psychotherapy and pharmacotherapy. The use of psychotherapy for treatment of BPD has been well-established, the effectiveness of pharmacotherapy remains less clear.

OBJECTIVES: To evaluate the effectiveness of olanzapine and fluoxetine on outcomes (including depression, anxiety, anger/impulsivity/aggression and global assessment of functioning) of BPD patients. SEARCH STRATEGY: Searched PubMed for the terms "fluoxetine" and "borderline personality disorder" and "olanzapine" and "borderline personality disorder". SELECTION CRITERIA: Only included randomized controlled trials in the English language that focused primarily on objective as stated above. MAIN RESULTS: Two fluoxetine studies included in this review, only one study showed significant improvement in depression and anger in BPD patients receiving fluoxetine but this was small (approximately 20%). Both studies showed significant improvement in global assessment of functioning (GAF) in fluoxetine groups. Four olanzapine studies included in this review, 3 compared olanzapine to placebo and 1 compared olanzapine to a mixed olanzapine-fluoxetine combination (OFC) to fluoxetine. In 2 of the 3 olanzapine studies, there was significant improvement in depression, anxiety and GAF, improvements ranged from 21%-39% for depression and anxiety. All 3 olanzapine studies show improvement in anger/impulsivity/aggression (highest improvement was 49%). In the mixed study, OFC and olanzapine group showed significant improvement in depression and anger but this improvement was mild. Anxiety and GAFwere not measured in

the mixed study. CONCLUSIONS: Overall, fluoxetine leads to mild improvement in depression, anger and GAF. Olanzapine treatment of BPD patients leads to mild-moderate improvement in depression, anxiety, anger/impulsivity/aggression and GAF.

Introduction

Borderline personality disorder (BPD) is a chronic psychiatric disorder that is characterized by marked impulsivity, instability of mood and interpersonal relationships. Patients are said to stand on the border between neurosis and psychosis[1].

Many studies have shown that dialectical behavioral therapy (DBT) is effective in improving outcomes for BPD. These outcomes include depression, anxiety, interpersonal functioning, social adjustment, global psychopathology and self-mutilation[2]. However, effectiveness of pharmacotherapy remains less clear.

In order to determine the main pharmacological therapies in use for BPD patients, I performed a search using the PubMed database and the terms "borderline personality disorder" and "pharmacotherapy". These terms identified 51 articles. The majority of the articles included agents in use ranging from neuroleptics (typical and atypical), serotonin reuptake inhibitors (SSRIs) and other antidepressants, mood stabilizers, benzodiazepines and MAOIs. My goal was to determine which agents were more effective than placebo in improving the BPD outcomes, including depression, anxiety, impulsivity/aggression and a complete assessment of psychiatric functioning-global assessment of functioning.

Epidemiology

The prevalence of BPD is approximately 2% in the general population[3]. About 75% of these are women. BPD occurs in association with other axis 1 disorders including mood disorders, substance abuse, eating disorders and post-traumatic stress disorder. Zanarini et al[4] conducted a study in 1998 to assess the

lifetime occurrence of a full range of DSM-III-R axis I disorders in a group of patients with criteria-defined borderline personality disorder and comparison subjects with other personality disorders. They found that of 504 inpatients with personality disorders the majority of them had concurrent axis I disorders. In particular, of the 379 patients meeting DSM-III-R (*Diagnostic and Statistical manual of Mental Disorders,* 3rd edition revised) criteria for BPD, 1% had psychotic disorders, 10% had somatoform disorders, over 80% had anxiety disorders and over 90% had mood disorders. They also found that significantly more men had substance abuse than women (82% versus 59%) and significantly more women then men had eating disorders (62% versus 21%). Significantly more women were likely to have PTSD than men (61% versus 35%)[4].

Paris has reported that BPD patients have a high rate of suicide when they have concomitant alcohol abuse or mood disorders[3]. The high prevalence of these axis I disorders in BPD patients makes it more likely that a large proportion of BPD patients will be suicidal.

Diagnosis

According to the *Diagnostic and Statistical manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) the diagnosis of borderline personality disorder can occur in early adulthood when an individual shows at least five of the criteria listed below:

A pervasive pattern of instability of interpersonal relationships, self-image, and the affects, and the marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

Affective symptoms
-Affective instability due to marked reactivity of mood (e.g., intense episodic dysphoria, irritability or anxiety usually lasting a few hours and only rarely more than a few days)
-Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
-Chronic feelings of emptiness
Impulsive symptoms
-Recurrent suicidal behavior, gestures or threats, or self-mutilating behavior
-Impulsivity in at least 2 areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating)
-A pattern of unstable and intense personal relationships characterized by alternating between extremes of idealization and devaluation
Interpersonal symptoms
-Frantic efforts to avoid real or imagined abandonment
-Identity disturbance: markedly and persistently unstable self-image or sense of self
Cognitive symptoms
-Transient, stress-related paranoid ideation or severe dissociative symptoms

**Paris has grouped the criteria based on the basic trait dimensions (affective, impulsive, interpersonal and cognitive)*[5].

Despite the criteria set forth by the DSM-IV for the diagnosis of BPD, the diagnosis is still difficult to make. Paris has addressed a number of factors that account for this[4]. One of these is the wide range of symptoms seen in BPD that are typical of other axis 1 disorders including mood and anxiety disorders which may lead BPD patients to be misdiagnosed. Additionally, patients may also have concurrent axis 1 disorders in addition to the BPD, leading to their BPD going undiagnosed as their axis 1 disorders are being treated[5].

The diagnosis of BPD therefore relies not only on relying on the DSM-IV criteria but also a good and long term relationship with a patient such that the clinician can recognize the multiplicity and chronicity of symptoms[5]. Clinicians

are often forced to rely on information from family members, friends and other health care provides making the diagnosis even more complex[5].

Natural course and prognosis

The management of BPD patients is difficult for psychiatrists and other physicians because these patients present with chronic suicidality, including multiple suicidal threats and attempts over years. What is even more troubling for physicians is that about 1 in 10 BPD patients eventually succeed in completing suicide[5]. Predicting which BPD patients will commit suicide is difficult and about 90% of patients improve despite threatening to complete suicide on multiple occasions [5]. Moreover, overzealousness on the part of the physician to hospitalize BPD patients when they threaten or act suicidal can be counterproductive and reverse any progress that had been made[6].

In spite of this chronic suicidality, most patients with BPD improve over time. Approximately 75% of BPD patients will have nearly normal functioning by the age of 35 to 40 years and 90% will recover by the age of 50. While the mechanism of recovery is unclear, it has been shown that with increasing age of BPD patients, there is a decrease in impulsivity and an avoidance of stressful interpersonal relationships[5].

Treatment

In his commentary on the American Psychiatric Association Guidelines (APA) for the treatment of BPD, Paris has commented on the use of both psychotherapy and pharmacotherapy[6]. The mainstay of treatment for BPD continues to be psychotherapy[6]. While there has been some use of psychoanalytic

therapy in the treatment of BPD patients, there has been ample evidence for the use of dialectical behavior therapy (DBT) particularly in an outpatient setting[6].

DBT draws upon supportive, cognitive and behavioral therapies. It was developed by Marsha Linehan who based her theory on the inability of BPD patients to identify emotional experiences and tolerate frustration or rejection. The main functions of DBT are (1) enhance and expand patient's skillful behavioral patterns, (2) improve patient's motivation to change, (3) ensure that the new behavioral patterns generalize from the therapeutic to the natural environment (4) structure the environment so that effective

behaviors are reinforced, and (5) to enhance the motivation and capabilities of the therapist so that effective treatment is rendered[1]. DBT includes individual and group therapy with homework assignments also forming part of the treatment. DBT has been shown to be effective with an improvement in interpersonal relationships and decreased parasuicidal behaviors[1].

The effectiveness of DBT suggests that what BPD patients benefit most from is the development of a practical relationship with another human being. Nevertheless, DBT is very resource-intensive, time consuming and expensive. There is thus a need to determine if other treatments exist for those who are unable to participate in DBT or who need an additional supplement to DBT or for those admitted to hospitals who only require treatment for a short time. Accordingly, various pharmacotherapies have been suggested in the treatment of BPD. When used as an adjunct to DBT, pharmacotherapy may aid in the relief of symptomatic distress associated with BPD. For instance, antipsychotics are used

to treat cognitive/perceptual symptoms, SSRIs to treat affective dysregulation and mood stabilizers for impulse-behavioral dyscontrol[6].

Currently, no algorithms have been established for the pharmacotherapy of BPD. In many axis 1 disorders such as depression, algorithms have been useful since there is an established effective treatment which allows the clinician to be able to modify therapy for treatment-resistant cases. The APA guidelines have been unable to make clear what medications are effective for BPD[6]. As a result, many BPD patients end up receiving multiple medications. A prospective study by Zanarini et al found that 40% of borderline patients were taking 3 or more concurrent psychiatric medications over 6 years of follow up, 20% were taking 4 or more concurrent psychiatric medications and 10% were taking 5 of more[7].

There is a need to minimize polypharmacy for BPD patients by determining whether particular medications would produce the most benefit. Additionally, clarification of the effectiveness of particular medications would provide the evidence basis for the use of BPD management algorithms. Finally, use of this research would provide an opportunity to use these medications in the presence of a stable and effective DBT program in order to have a more pronounced effect.

Given the risk of impulsive medication over-use by this population, I decided to limit my findings to those agents that were safe. I excluded medications that had a high risk of death from overdose (ex. tricycylic antidepressants have high risk of death from overdose), high risk of abuse (benzodiazepines), significant side effects (typical neuroleptic haldol), or needed

more frequent monitoring (atypical antipsychotic clozapine). I only considered those agents that were both safe and that had been tested using randomized controlled trials. This left me with two main agents: the atypical antipsychotic olanzapine and a selective serotonin reuptake inhibitor (SSRI) fluoxetine.

I conducted a systematic review to address the following question: Is olanzapine or fluoxetine or a combination of the two more effective than placebo in improving the outcomes (as measured by depression, anxiety, impulsivity/aggression, and a complete assessment of psychiatric functioning-global assessment of functioning) of BPD patients?

Systematic Review of the Literature

Selection of Articles

To identify relevant articles, I searched the PubMed database using the terms "borderline personality disorder", "olanzapine" and then "borderline personality disorder", "fluoxetine". Searches were limited to those in the English language. I supplemented these sources by searching the Cochrane Library database for the terms "borderline personality disorder" and "treatment".

All abstracts were reviewed. Articles that did not primarily focus on the treatment of borderline personality disorder symptomatology were excluded because their focus did not address the question at hand. Bibliographies of articles that were not excluded were hand-searched and articles that were relevant to the pharmacotherapeutic treatment of borderline personality disorder using olanzapine, fluoxetine or both were reviewed. Inclusion of a comparison group

was required. Studies that were not double-blinded randomized clinical trials and reviews that were nonsystematic were excluded.

Studies were also limited to those including the diagnosis of BPD based on the DSM-IV or DSM-IIIR criteria for BPD, or DSM-IV or DSM-III-R and Diagnostic Interview for borderlines (DIB-R) criteria for borderline personality disorder. Studies had to have outcomes that included depression, anxiety, anger/impulsivity or assessment of functioning.

The search for "borderline personality disorder", "olanzapine" yielded 17 articles of which 4 articles met inclusion criteria. Whereas, the search for "borderline personality disorder", "fluoxetine" yielded 28 articles of which only 2 articles met inclusion criteria. Table 1 shows the articles that were selected.

Appraisal of the Randomized controlled trials of the treatment of BPD patients with olanzapine, or fluoxetine, or both

Internal Validity

Of the 6 articles selected, their quality was judged according to a 0-3 scale checklist (0=poor, 1=fair, 2=good, 3=excellent) and potential for bias (ø means no bias represented by 3, + means low potential for bias rep. by 2, ++ higher potential for bias rep. by 1, +++ highest potential for bias rep. by 0). The categories considered included representativeness of study population; potential for selection bias, measurement tool-equal, reliable and valid; potential for confounders; appropriate analysis; outcome-adequately described with

significance. Perfect score would be 18 (a score of 3 for each category measured). Table 2 shows there results.

Selection of study population

Studies were assessed based on whether they selected an appropriate study population. Studies that were rated as excellent included a study population that met the DSM-IV or DSM-III-R criteria for BPD and a study population that was more homogenous. The inclusion of a homogenous study population should lead to the detection of an effect (even if small) in the treatment group if one exists.

Of the two fluoxetine studies, the study by Salzman et al received a good rating because they only included patients with BPD identified using DSM-IV criteria. In contrast, the study by Simpson et al received an excellent rating not only because they included study participants with BPD (according to DSM-IV criteria) but they also tried to only include those BPD patients who had affective and impulsivity behavioral components to their condition. This improved the homogeneity of the study population

because of the selection of individuals who would benefit from the intervention (fluoxetine). Fluoxetine is expected to improve affective and impulsive symptoms. However, some BPD patients also have identity disturbance symptoms, which would not improve with fluoxetine[8].

Another criterion that was used in evaluating the appropriateness of the study population was the drop out rate. Studies with a high drop out rate received a lower rating than those with a low drop out rate since high drop outs lead to a

decreased ability to detect an effect in the treatment group. Both the fluoxetine studies had low drop out rates, with retention of approximately 80%. The study by Salzman et al included a run-in period that improved compliance in the study with 81.5% of study participants completing the study. In the Simpson et al study, 80% of the individuals completed the study even though there was no run-in period. The low drop out rate in this study is probably because the post-treatment assessment was carried out at 10 weeks which was before the end of the study (at 12 weeks) [8]. One of the components of BPD is "frantic efforts to avoid real or imagined abandonment". If individuals in the study were aware that the study was about to end, they could have engaged in actions to deal with their fear of abandonment such as dropping out of the study.

Unlike the fluoxetine studies, high drop out rate was a major problem in two of the olanzapine studies (the 2001 Zanarini & Frankenburg study and Bogenschutz & Nurnberg study). All the olanzapine studies used the DSM-IV criteria to establish a diagnosis of BPD. There were no attempts made to improve homogeneity of the study

population. The studies by Zanarini, Frankenburg (2001) and Bogenschutz & Nurnberg had higher drop out rates than the other two olanzapine studies (the 2004 Zanarini et al study and the Soler et al study) [10, 11, 12,13].

Zanarini, Frankenberg (2001) report on a 6 month trial with 28 women with BPD. At the end of the trial only 9 subjects remained. Of the 19 subjects initially assigned to olanzapine treatment and the 9 assigned to placebo, only 8 (42.1%) remained in the olanzapine group and only 1(11.1%) remained in the

placebo. The primary reason cited for this high rate of discontinuation in both the olanzapine and placebo groups was loss to follow up. Other reasons cited included side-effects such as perceived weight gain, increase in depression or anxiety in the olanzapine group and increased depression in the placebo group[10]. The high drop out rate in this study could account for the lack of improvement on all outcome measures in the olanzapine group at the end of the study.

In the study by Bogenschutz and Nurnberg, there were also high drop our rates. Of the 40 BPD patients who initially enrolled in the study only 23(57.5%) remained at the end of the 12 weeks. Reasons for termination in the olanzapine group were loss to follow up (10%, N=2), lack of efficacy (10%), weight gain (10%), sedation (10%) and patient's violation of protocol (10%). In the placebo group, reasons for termination were loss to follow up (25%, N=5) and lack of efficacy (10%) [11]. This high drop out rate could explain the lack of positive outcome results in the olanzapine group at end point (12 weeks).

The study by Zanarini et al (2004) and that by Soler et al had high compliance. The short duration of study (8 weeks) in the Zanarini et al (2004) trial may have helped to reduce the drop out rate. Of the 45 subjects who began the study 42 (93%) remained at the end of the study[12]. In the Soler et al study there was a 4-week selection phase that ensured that of the 60 patients who began the study, 42 subjects (70%) completed the 12 week study[13]. The low drop out rates in these studies accounts for the larger positive effect seen in the olanzapine treated group on all the outcome measures that were assessed.

Selection Bias

Among the olanzapine studies, those that had the highest drop out rate had the greatest potential for selection bias. In the Zanarini, Frankenburg (2001) study analysis was done on treatment-completers (not intent-to-treat basis) and of those individuals who completed treatment more patients were lost in the olanzapine-treated group than the placebo group (42.1% remained in olanzapine group versus 11.1% in placebo group)[9]. This could have resulted in an overestimation of the effect of olanzapine on BPD symptoms. In particular, having only one patient in the placebo group at the end of the study precludes a reasonable comparison between the olanzapine treated group and the placebo group.

The study by Bogenschutz and Nurnberg began with 20 patients in the olanzapine group and 20 in the placebo group. Analysis was based on treatment-completers (not intent-to treat basis). At the end of the study, there were more patients in the placebo (13) than the olanzapine group (10) [11]. The number of individuals remaining is nearly similar in both groups and the effect is not as profound as the Zanarini, Frankenburg study (2001). Nevertheless, this difference may have led to an underestimation of the effect of olanzapine on BPD symptoms.

In the 2004 study by Zanarini et al the shorter duration of the study reduced the drop out rate thus reducing selection bias. There were no differences between the fluoxetine, olanzapine and combined olanzapine fluoxetine groups with regard to psychiatric symptoms (OAS-M and MADRS) at baseline[11]. However, even though the authors report that there were no demographic

differences between the groups there is no information provided with regard to the number of individuals in each group (olanzapine and placebo) based on demographic characteristics.

The study by Soler et al was the most effective at reducing the potential for selection bias among the olanzapine studies. They randomly assigned individuals after the selection phase in a 1:1 ratio to receive DBT plus olanzapine or DBT plus placebo. Randomization was effective and individuals were similar in both groups with regard to age, gender, number of DBT sessions attended and measures of psychiatric illness. They were also similar with regard to medications that they took-benzodiazepines and antidepressants. Individuals differed only with regard to numbers taking mood stabilizers. 10 individuals in the DBT plus olanzapine group took mood stabilizers and only 5 in the DBT plus placebo group were on mood stabilizers[13]. This may have made the positive effects of the DBT plus olanzapine treatment more profound.

The fluoxetine studies did not have such a high potential for selection bias as some of the olanzapine studies. In the study by Salzman et al there was enough demographic information provided to compare the fluoxetine and placebo groups. The groups were comparable in terms of age, race, marital status, education (years of school), prior psychiatric treatment and psychiatric symptoms (DIB-R). Groups differed slightly with regard to the number of women in both groups, with the fluoxetine group having 10 women compared to the 4 in the placebo group[9].

The Simpson et al study also did a good job at reducing selection bias. The fluoxetine and placebo group were comparable in terms of demographic

characteristics and psychiatric symptoms (SCID-II symptoms endorsed). In addition, in this study they included demographic and psychiatric symptoms information on drop outs. There were no profound differences between the dropouts and the completers of the study. Completers of the study in the fluoxetine and placebo groups did have slight differences with regard to marital status, ethnicity and age. In the fluoxetine group there were 3 married individuals and none in the placebo group, 3 single/never married in the fluoxetine group compared to 7 in the placebo. Individuals in the fluoxetine group were slightly older-mean age of 39.79 versus 32.73 in the placebo group. More individuals in the placebo group were white (10) compared to the fluoxetine group (6). It is unclear whether these demographic differences had any effect on the results.

Measurements and measurement bias

All but one of the studies in this review used the DSM-IV criteria for the diagnosis of BPD in measurement of the exposure. The Salzman et al study used the DSM-III-R criteria for diagnosis of BPD which are very similar to the DSM-IV. The DSM-III-R criteria differ in the definition of affective symptoms as shown below[14].

-Affective instability: marked shifts from baseline mood to depression, irritability, or anxiety, usually lasting a few hours and only rarely more than a few days

-Chronic feelings of emptiness or boredom.

In addition, the DSM-III-R criteria do not include "*Transient, stress-related paranoid ideation or severe dissociative symptoms*" which is included in the DSM-IV criteria.

Various self-report and observer assessments were used to measure outcomes in the studies (see table 1). The outcome measures included specific measurement of various psychiatric symptoms as well as an overall assessment of functioning. The observers used to measure outcomes in all the studies included in this review were blinded.

Both the fluoxetine studies used a combination of subjective and objective outcome measures. The reliability of the objective measure of global assessment of functioning (GAF) in the Simpson et al study is questionable. The GAF was calculated using the combined means of the therapist-rated GAF and psychiatrist-rated GAF. However, these values differed at baseline with the therapist-rated GAF showing no difference between the DBT/placebo group and the DBT/fluoxetine group. But the psychiatrist-rated GAF was significantly higher (approximately 10 points) for those in the fluoxetine group compared to the placebo group at baseline. This increase on GAF at baseline may have influenced the results such that at the end of the study no significant improvement was found in overall assessment of functioning in the DBT/fluoxetine group[8].

Of the outcome measures used in the Salzman et al, it would have been important to determine the validity and reliability of the PDRS (Personality Disorder rating Scale) particularly because it was created in this study to assess anger and depression. Nevertheless, the study designers also incorporated other subjective and objective measures of anger and depression including the OAS-M, POMS and HAM-D, the validity and reliability of which have been shown in other studies.

Regarding the two fluoxetine studies, the Salzman et al study utilized frequent measurements (weekly throughout the 13 week duration of the study) while the Simpson et al study only used two measurements. This frequent monitoring may have made it easier to detect an effect in the fluoxetine group in the Salzman et al study. Whereas, in the Simpson et al study, less frequent measuring made it impossible to detect an effect[8, 9].

In two of the olanzapine studies, the 2001 Zanarini and Frankenburg study and the Bogenschutz and Nurnberg study there was a measurement of both subjective and objective outcome measures. The other two studies (the 2004 Zanarini et al trial and the Soler et al trial) did not use self-report measures. The inclusion of subjective measurements of outcome would have been helpful because these are an important component of personality disorder diagnosis and prognosis. Not including subjective measures probably led to a reduction in the effect observed in the medication groups.

Three of the olanzapine studies conducted in the United States (the 2001 Zanarini and Frankenburg, the 2004 Zanarini et al study and the Bogenschutz and Nurnberg study) include an assessment of side effects. This is important because the occurrence of side effects affects the recommendation of olanzapine for the treatment of BPD. Additionally, the dose of olanzapine and the timing (from the onset of treatment) when these side effects occur is important in this recommendation[10, 11, 12].

Statistical Analysis, confounding

Analysis in the Simpson et al study was done on treatment-completers while that in the Salzman et al study was done on intent-to-treat basis. Each study employed a one-way analysis of variance (ANOVA) on the outcome measures at pretreatment and postreatment to determine differences between fluoxetine and placebo groups. Both studies received a rating of 2 (good) for the analysis. The study by Simpson et al received a rating of + (2=good) for the potential for confounding. The study by Salzman et al received a fair rating because of the higher potential for confounding in this study[8, 9].

With regard to the olanzapine studies, only the Soler et al study incorporated intent-to-treat analysis[13]. Both the Soler et al and the Bogenschutz and Nurnberg studies used ANOVA and ANCOVA. In the Zanarini studies, the 2001 study utilized Fischer exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Random effects regression was then used to assess between-group differences in outcomes. In the 2004 Zanarini et al study, analyses were carried out using the logistic
regression model for categorical variables and multiple regression for continuous variables. Three of the olanzapine studies received a quality rating of ++ (1=fair) with regard to potential for confounding. The Soler et al study received a rating of + (2=good) because of the lower potential for confounding[10, 11, 12, 13].

Other Limitations

Overall these studies included small samples and therefore may not be powered enough to detect a larger positive effect of the medication (olanzapine or

fluoxetine) on BPD symptomatology if this exists. Also, a number of studies had a high drop out rate, further increasing the risk of bias. These limitations are not surprising—the nature and characteristics of BPD patients make it difficult to have a trial with a significant number of patients if one excludes individuals with axis I disorders, those who receive psychotherapy, and those not on psychiatric medications. Also, including these individuals in a trial can sometimes dilute the effect of the medication on BPD symptoms or complicate the result[15]. At the same time, these sampling characteristics limiting internal validity actually improve external validity—many BPD patients suffer from axis I disorders and many patients receive 4-5 psychiatric pharmacological agents with all the side effects of these agents[15].

-Fluoxetine Studies

In the Simpson et al study they took an important component into account - the inclusion of DBT within the clinical trial. At the end of the study, they found that DBT/placebo group did better than the DBT/olanzapine group. This result can be explained by the inclusion of therapy in this study overwhelming the effect of the medication[8].

Additionally, the authors of this study note that they may have been a bias towards medication nonresponders because participants in this study were willing to discontinue current medications and risk assignment to placebo. However, it is worth mentioning that many of those who dropped out did so because of being unable to tolerate a nonmedicated condition[8].

The study population in the Simpson et al study consisted of hospitalized individuals with axis I disorders. The authors note that even though there were no patients with bipolar disorder in this study, there could have been some individuals with BPD who had an undetected and subclinical form of bipolar disorder. Prescribing these individuals antidepressants could have worsened their condition explaining the lack of effect in the DBT/fluoxetine group[8].

In the Salzman et al study, they also obtained some placebo responsiveness in their sample. They thus decided to refine their analyses and include a measure of placebo responsiveness. After creating a measure of placebo responsiveness they used it as a covariate in a series of repeated measures analyses of covariance (ANCOVAs) [9].

The Salzman et al study included individuals with mild or moderate BPD who were relatively high functioning at baseline. This may have affected their results since the only significant differences were those on the POMS anger subscale. Perhaps, the inclusion of individuals who were already high functioning nullified the effects of fluoxetine[9].

-Olanzapine studies

In the Soler et al study, BPD participants were allowed to continue treatment with some medications (benzodiazepines, antidepressants, and mood stabilizers) that they were on before the trial. However, the doses of the medications could not be adjusted while in the trial. Of note, more patients in the DBT/olanzapine group were on mood stabilizers (N=10) compared to those in the

DBT/placebo group (N=5). This could have accounted for the positive effect seen in the DBT/olanzapine group[13].

Participants in the Soler et al study were also allowed to continue the use of toxic substances. The authors make no mention of what toxic substances were included or the distribution of those taking toxic substances in the DBT/olanzapine or DBT/placebo groups. This could have biased the results in this study[13].

Even though allowing study participants to continue their psychiatric medication or toxic substances allows for the applicability of these results to characteristic individuals with BPD, it nevertheless may influence the results within the trial so that in the case of the Soler et al study the effect of olanzapine was actually greater than that seen within the study[13].

In the Bogenschutz and Nurnberg trial, study participants were allowed to continue ongoing psychotherapy provided that this had began more than 3 months before randomization. There is no mention of what kind of therapy study participants were engaged in. The authors do note that only a few individuals within the study were involved in therapy (1 in the olanzapine group and 4 in the placebo group). However, there was a high drop out rate in this study. As a result, even though only 5 individuals were involved in therapy, they could have affected the results through an underestimation of the effect of olanzapine[11].

In the 2004 trial by Zanarini et al, they failed to include a placebo group. Thus while comparisons can be made between taking olanzapine or fluoxetine or

a combination of olanzapine and fluoxetine, nothing can be said about how this compares to individuals who are not taking these psychiatric medication[12].

The duration of the trial in all these studies was short. Study duration ranged from 12 to 13 weeks in the fluoxetine studies and 8 weeks to 24 weeks in the olanzapine studies[8, 9, 10, 11, 12, 13]. This makes conclusions from these trials difficult to apply to BPD patients whose condition is much more chronic.

Some studies such as the Soler et al study and the 2004 Zanarini et al study included only self-rated assessments of outcome whereas others included both self-rated and observer assessments of outcome. Including both self-rated and observer assessments increases the validity of the results compared to just self-rated assessments or observer assessments because of the characteristics of BPD patients including the fear of real or imagined abandonment.

Outcomes Fluoxetine Studies

Depression

The two fluoxetine studies in this review reported depression as an outcome but the results were mixed. The Salzman et al study showed a significant decline in a self-reported depression scale (POMS) in the fluoxetine group versus the placebo group (see table 1). There was no significant decline in observer rated scales (HAM-D and PDRS). In the Simpson et al study, the DBT/placebo group showed significant improvement on the BDI scale compared to the DBT/fluoxetine group[8,9].

Anxiety

The only fluoxetine study that measured anxiety was the Simpson et al study and this result did not show improvement in anxiety. Among the DBT/fluoxetine group in the Simpson et al study, there was no significant difference in the STAI compared to the DBT/placebo group[8]. The Salzman et al study did not measure anxiety[9].

Anger, Impulsivity and Aggression

Both the fluoxetine studies measured anger but the results were mixed. In the Salzman et al study there was a significant decline in POMS and PDRS (self-reported) anger scales in the fluoxetine group compared to the placebo group as shown in table 1. Results of the Simpson et al trial on the other hand indicate near significant improvement in the DBT/placebo group compared to the DBT/fluoxetine group on anger measurements[8,9]

Assessment of Functioning

In both the fluoxetine studies there was improvement in functioning. GAS scores improved significantly in the Salzman et al study. There was a significant improvement in GAF scores in the Simpson et al study as can be seen in table 1[8,9].

Outcomes Olanzapine and Mixed Studies

Depression

In the three studies comparing olanzapine to placebo (Bogenschutz and Nurnberg study, 2001 Zanarini and Frankenburg study and the Soler et al study) only 2 showed an improvement in depression[11, 13]. In the Soler et al study, the

DBT/olanzapine group did significantly better than the DBT/placebo group on the observer rated HAM-D at the end of the study period (12 weeks) [13]. In the Bogenschutz and Nurnberg study, the olanzapine group did significantly better than the placebo group at 8 weeks on the HAM-D scale, but this benefit was not significant at the end of the study (12 weeks) [11]. Unlike the two studies mentioned above, the 2001 Zanarini and Frankenburg study did not show significant change in SCL-90 depressive symptoms at the end of study period which was 24 weeks[10].

The 2004 Zanarini et al study comparing olanzapine, fluoxetine and a combination of olanzapine and fluoxetine (OFC) showed that OFC and olanzapine groups did better than the fluoxetine group on observer-rated MADRS scale for depression. The olanzapine group also did much better than the fluoxetine group on the MADRS scale[12].

Anxiety

The three olanzapine studies measured anxiety as one of their outcomes (the Soler et al study, Bogenschutz and Nurnberg study and the 2001 Zanarini and Frankenburg study). The results were mixed. In the Soler et al study, the DBT/olanzapine group did better on the HAM-A compared to the DBT/placebo group as shown in table 1. The Bogenschutz and Nurnberg study showed no significant changes in HAM-A scales at end point but significant changes in the olanzapine group compared to placebo at 8 weeks[11]. The 2001 Zanarini and Frankenburg study also showed that symptoms improved in the olanzapine group compared to placebo at the end of the study on SCL-90 symptoms of anxiety[10].

The 2004 mixed study by Zanarini et al did not measure anxiety as one of their outcomes[12].

Anger, Impulsivity, Aggression

All three olanzapine studies also showed an improvement in anger, impulsivity and aggression for BPD patients treated with olanzapine compared to placebo. In the Soler et al study, the DBT/olanzapine group showed a greater decrease in impulsivity/aggressive behaviors compared to DBT/placebo group[13]. In the Bogenschutz and Nurnberg study, there was a significant improvement on the AIAQ at 8 weeks but this was not significant at the endpoint as seen in table 1. In the 2001 Zanarini and Frankenburg study, there was significant improvement in the SCL-90 symptoms of anger/hostility and interpersonal sensitivity[10].

The 2004 mixed study by Zanarini et al showed that the OFC and olanzapine groups showed significant improvement on the OASM compared to fluoxetine. No significant difference was found between the OFC and olanzapine groups on this measure[12].

Assessment of Functioning

In the two olanzapine studies (the Soler et al study and the Bogenschutz and Nurnberg study) where assessment of functioning was done, there was an improvement in the olanzapine group as seen in table 1. In the Soler et al study, the DBT/olanzapine group experienced significant improvement in the CGI scale[13]. In the Bogenschutz and Nurnberg study, there was a significant improvement in the GAF scores at 4 and 8 weeks but not at endpoint[11]. Due to the

small number of participants in the 2001 Zanarini and Frankenburg study; there was no report on the GAF scores of the study population at endpoint[10].

In the mixed study, there was no assessment of overall functioning at the end of the study. The only assessment that was done was at the beginning of the study and included the mean GAF at baseline which was found to be at the low end of fair.

Side Effects

All the olanzapine studies reported a number of side effects associated with the olanzapine group. The most common symptom was weight gain in all 3 olanzapine studies; this was significant[10, 11, 13]. The average amount of weight gained varied by study- 2.87lbs (2001 Zanarini and Frankenburg study), 8.25 lbs (Bogenschutz and Nurnberg study) and 6.03lbs (Soler et al study. In the 2004 Zanarini et al study (mixed study), there was no significant weight gain in the olanzapine group compared to the fluoxetine group[12]. Other side effects that were noted included increase in cholesterol levels, sedation and mild akathisia[10,11,12,13].

Summary of Internal Validity

Both fluoxetine studies received a good quality rating. The quality of the olanzapine studies varied from fair to good as shown in table 2. All the studies were affected by small sample sizes which diminished the power of the study. The Soler et al study had the largest sample size (60) which, while better than the studies with 20 individuals, was still under-powered. Additionally, some of the

studies suffered from a high degree of selection bias following the unequal drop out rates in intervention versus placebo groups particularly in two of the olanzapine studies (the 2001 Zanarini and Frankenburg study and the Bogenschutz and Nurnberg study).

None of the studies reviewed received an excellent rating on measurement. This was because they suffered from measurement bias. In some of the studies, the reliability and validity of the measurement tool were not assessed. Most of the studies used self-reports which have been shown to be unreliable. However, they also included observer rated scales which improved the validity of the assessment tool used.

Finally, there was a small potential for confounding in all the studies even though they were all randomized studies. It was unclear if randomization was done well in all the studies and even when done appropriately the high and unequal drop out rate in some studies introduced some confounding.

External Validity: generalizability to other BPD patients

Of the fluoxetine studies that were reviewed, the Simpson et al study had the greatest external validity. In this study, they included patients diagnosed with BPD and concurrent Axis I disorders. Individuals with BPD are frequently susceptible to a spectrum of axis I disorders including affective disorders, anxiety disorders, eating disorders and substance abuse disorders[16]. Excluding these individuals from a trial frequently limits the results to a minority of patients.

The Simpson et al study also included DBT for both the fluoxetine and placebo groups[8]. This makes their results generalizable to an external BPD population. Zanarini et al reported in their 2004 study on mental heath service utilization that over 80% of the BPD patients in their study population were involved in some form of psychotherapy[7]. They also found that about 73% of BPD patients continued to use outpatient psychotherapy in a sustained manner through their 6 year follow up period[7]. Developing a study that incorporates therapy is an essential component of making the results generalizable since many BPD patients are involved in therapy.

The external validity of the other fluoxetine study (the Salzman et al study) was limited by the inclusion of BPD patients with only mild to moderate symptoms. These results cannot be generalized to all BPD patients, some of whom may not be as high functioning as those individuals included in this study.

Of the olanzapine studies reviewed, the Soler et al study was most generalizable to an external population of BPD patients. Study participants included individuals who were already on psychiatric medications including benzodiazepines, antidepressants and mood stabilizers. Doses could not be modified while in the study. Additionally, participants could continue the use of toxic substances as long as they did not fit dependence criteria. Both the olanzapine and placebo groups also had DBT included in their regimen[13]. Many BPD patients are already on psychiatric medications for their BPD symptoms and have a high potential for substance abuse. The inclusion of more characteristic BPD patients improves the external validity of this study. However, the results of

the Soler et al study are not generalizable to inpatients or individuals with active Axis I disorders since these were exclusion criteria in this study.

Both the 2001 Zanarini and Frankenburg study and 2004 Zanarini et al study had limitations with regard to their external validity. Among these limitations was the exclusion of individuals with axis I disorders, the exclusion of men, the exclusion of any individuals who were on any psychiatric medications or who were taking any toxic substances(alcohol or drugs) and the exclusion of individuals who were acutely suicidal.

The Bogenschutz and Nurnberg study was applicable to both men and women with BPD since these individuals comprised the study population. Additionally, in this study individuals who had already began psychotherapy 3 months prior to randomization were allowed to continue with this, which improves the external validity.

All the studies above were of short duration from 8-24 weeks. This makes it difficult to generalize results to BPD patients who need maintenance as well as acute management of their symptoms. Whereas, evidence for the effectiveness of maintenance therapy in many axis I disorders such as bipolar is available, similar evidence for BPD is lacking from these studies[17].

Discussion

There is sufficient data to date that shows the effectiveness of DBT in the treatment of BPD. Less sufficient data exists for the effectiveness of pharmacotherapy. However, the use of pharmacotherapy in the treatment of BPD

is important for a number of reasons. Among them is the treatment of BPD patients in an inpatient setting where the stay is short, as well as the complexity of BPD symptomatology that may necessitate the use of interventions that can provide quick responses, such as pharmacotherapy[18]. In the case of outpatients, both psychotherapy and pharmacotherapy are essential in helping to keep patients out of the hospital and functioning well[18]. There is therefore a need to determine which pharmacotherapy is best and under what circumstances for BPD treatment.

The American Psychiatric Association guidelines on the treatment of borderline personality disorder highlight the basis for use of pharmacotherapy in these patients[19]. First, medications cannot be used as a cure for borderline personality disorder. Pharmacotherapy can only be used to diminish symptoms and optimize functioning. Second, pharmacotherapy must target specific aspects of patient's behavior. Third, affective dysregulation and impulsive aggression requires specific attention because they are risk factors for suicidal behavior, self-injury and assaultiveness. Fourth, medications must target the neurotransmitter basis of behavior for both acute and chronic components. Finally, symptoms that are similar in both borderline personality disorder and axis I disorders can respond similarly to the same medication.

Fluoxetine in the treatment of BPD patients

The American Psychiatric Association (APA) recommendations focus on three behavioral dimensions of BPD patients. These include affective dysregulation, impulsive-behavioral dyscontrol and cognitive-perceptual difficulties. These recommendations focus on the availability of evidence to

determine the strength of medications in dealing with these behavioral dimensions. The medications considered include antidepressants, consisting of SSRIs (fluoxetine or sertraline) and serotonin reuptake-norepinephrine reuptake inhibitors (SNRIs; specifically, venlafaxine) and monoamine oxidase inhibitors (MAOIs); mood stabilizers; benzodiazepines; and neuroleptics. While there is no mention of atypical antipsychotics such as olanzapine in these 2001 recommendations[19], the olanzapine studies identified were all published following the APA recommendations.

The APA recommendations focus on the use of SSRIs for the initial treatment of affective dysregulation symptoms (including mood lability, rejection sensitivity, inappropriate intense anger, depressive "mood crashes" and temper outbursts) and impulsive-behavioral dyscontrol symptoms[19]. The results from the two fluoxetine studies in my review contradict this recommendation particularly with regard to depression and anger. The Simpson et al study did not show any improvement on measures of anger and depression in the fluoxetine treated group. The Salzman et al study showed improvement in depression and anger. However, even on the most rigorous distinguishing score—the POMS anger and depression rating—this improvement was small (not more than 20%) and may not be clinically significant. The lack of clinically significant improvement on anger and depression may be related to the low dose of fluoxetine used in the Salzman et al study (mean 40mg/day) compared to the doses as high as 60-80mg/day in the trials considered by the APA[9].

According to the APA, not all BPD patients will respond to fluoxetine and it is recommended that a patient be switched from one SSRI to another if the response is suboptimal[19]. A reasonable trial (at least 12 weeks) of the initial SSRI must be attempted before switching to another one. Individuals included in the Salzman et al study may have been unable to respond to fluoxetine and could have had a better response with another SSRI.

The Simpson et al study (only fluoxetine study to assess anxiety) did not show an improvement in anxiety for BPD patients treated with fluoxetine[8]. This is consistent with the APA guidelines that call for the use of benzodiazepines since SSRIs may not be sufficient at controlling anxiety[19].

The APA evaluated other antidepressants such as MAOIs and tricyclic antidepressants that have been used to treat BPD patients. However, there isn't enough evidence to establish their effectiveness in a similar fashion to SSRIs. Additionally, the use of these other substances is problematic because of the side effects associated with them. SSRIs are associated with greater treatment adherence compared to MAOIs and tricyclic antidepressants because of their favorable side effect profile[19]. Furthermore, MAOIs and tricyclic antidepressants are much more lethal in overdose than SSRIs.

In one study evaluating the effectiveness of amitriptyline and haloperidol in the treatment of BPD patients, the authors reported an increase in suicidal ideation, paranoid thinking and assaultiveness in patients receiving amitryptyline[20]. This is particularly problematic in BPD patients who suffer from chronic suicidality and whose course is frequently marked by repeated suicide

attempts. Not increasing these patients risk of suicidality is fundamental to an effective treatment regimen.

Olanzapine in the treatment of BPD patients

In a systematic review by Grootens and Verkes to evaluate the effectiveness of atypical antipsychotics in the treatment of BPD patients, 4 antipsychotics were studied: clozapine, risperidone, quetiapine and olanzapine[21]. When the study by Grooken and Verkes was published, they only made mention of two placebo controlled trials evaluating the effects of olanzapine on outcomes for BPD patients. Both those studies were included in my review.

Much of the work that has been done on the use of pharmacotherapy for BPD has dealt with the serotonin pathway. The serotonin pathway is linked to the use of treatment of BPD symptomatology using antidepressants. Recently, the focus has changed to dealing with dopamine dysfunction and the subsequent use of atypical antipsychotics such as olanzapine. Friedel has postulated that dopamine dysfunction in BPD patients is linked to impulsivity, emotional dysregulation and cognitive-perceptual impairement[21]. Therefore using atypical antipsychotics would allow for improvement in these behaviors.

Compared with classical antipsychotics such as haloperidol and other atypical antipsychotic such as clozapine, olanzapine is associated with fewer side effects. Frankenburg and Zanarini reported that clozapine (an atypical antipsychotic) was effective in reducing symptoms in refractory BPD patients[23]. However, the use of clozapine is problematic because of the need to monitor white blood cell counts[23]. In the studies in this review the most significant side

effect for BPD patients on olanzapine was weight gain. Other side effects included high cholesterol, akathisia and sedation.

Overall, olanzapine studies suggest mild-moderate improvement in depression, anxiety, anger, impulsivity and aggression. The 2001 Zanarini study showed an improvement of 33.6% on SCL-90 anxiety scores within the first 4 weeks of the study which then became gradual (about 21%) over the remaining 5 months of the study[10]. The Soler et al study, which had the highest improvements in outcome, had only moderately significant results at best (39% improvement on the HAM-D, 31.3% on the HAM-A and 49.3% on behavioral reports of impulsivity and aggression) [13].

The dose of olanzapine used in these studies was 2.5 to 20 mg/day with study duration ranging from 8-24 weeks[10, 11, 12, 13]. There is a need to incorporate the results from these studies in APA guidelines for the treatment of BPD. Additionally, more work is needed with larger samples and over a longer period of time to establish the effectiveness of olanzapine in BPD treatment and to better appreciate the balance between benefits and costs.

Mixed Fluoxetine-Olanzapine combination in BPD patients

The mixed OFC group and olanzapine group produced greater improvement in depression, anger, impulsivity and aggression than the fluoxetine group. There is no benefit to using a combination of OFC compared to olanzapine from this study. Given the greater risk of side effects and costs with medication combination, these results suggest using only olanzapine. The improvements in

the olanzapine only group were clinically significant with 72.5% improvement on MADRS (depression) and 70.8% on OAS-M (aggression) [13].

This study did not include a placebo group, which would have been beneficial in order to make a more accurate comparison of their results. Additionally, more studies utilizing fluoxetine, olanzapine, OFC combination and placebo are needed together with DBT in all these groups to make results generalizable to a BPD population.

Directions for future research

In all the studies evaluated in this review there is great heterogeneity in study populations. Even though the primary focus is on BPD patients, some studies included patients with axis I disorders where others excluded these patients. Some studies allowed the study population to continue with their psychiatric medication or toxic substances where others did not. While this makes it difficult to compare the studies, it also points to the dramatic differences that exist between BPD patients seen in clinical practice[21].

Another problem with some of the studies included in this review is the high drop out rate. Even where drop out was not high, the size of the study population was small. There is a need for larger studies and long term follow-up of BPD patients in these trials.

Measurement tools that are used to understand the effectiveness of medications in the treatment of BPD need to be similar between studies. Trying to answer the question of effectiveness using different measurement tools makes comparison of studies difficult. Even when the outcome is the same e.g.

depression, the use of the same measurement tool between studies would make comparisons easier.

Comparing the effectiveness of different medications on one outcome measure in BPD patients is necessary to avoid polypharmacy of BPD patients. This does not mean that BPD patients cannot be on more than one medication to control symptoms. In fact various components of BPD symptomatology respond to different classes of medications. What is important is that current recommendations and practices incorporate evidence-based medicine.

It is important to establish the efficacy of trials for pharmacotherapy in BPD patients. One way in which this can occur is by including some component of psychotherapy such as dialectical behavioral therapy in outpatient medication trials of BPD patients. Doing so will allow these results to be generalizable to more BPD patients, many of whom are currently receiving outpatient psychotherapy.

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Table 1: Selected double-blinded, randomized-controlled trials for treatment of BPD using olanzapine, fluoxetine or both.

Study Authors, Year.	No.	Source Population	Study Population	Interventions	Outcome Measurement &Significant Results
Salzman, Wolfson, Schatzberg, Looper, Henke, Albanese, Schwartz & Miyawaki, 1995.	27	Community individuals with diagnosis of BPD. Volunteers	27 mild to moderately symptomatic volunteers with diagnosis of BPD. Sex-8 men, 14 women Age-mean 36y. Exclusions: Inpatient, h/o psychiatric hospitalization, recent suicidal behavior, concurrent secondary Axis II disorder, self-mutilating behavior (during past 4 years), major depression or Axis I disorder, present h/o substance abuse, use of psychotropic medication.	Fluoxetine; initial dose was 20g capsule, or identical placebo, and then doses titrated up to a max. of 60mg/ day as needed.	Measurements: -Evaluation by independent observers using Hamilton Rating Scale for Depression (HAM-D), Global Assessment Scale (GAS) & Personality Disorder rating Scale (PDRS). -Self-rated symptoms were assessed by use of the Profile of Mood States (POMS) and the McLean Hospital Overt Aggression Symptom Checklist(OAS-R) Results: -All subjects showed some improvement-60% on PRDS, 20% on POMS & 80% on HAM-D after using contingency table analyses. -Improvement in anger & depression in POMS for fluoxetine group compared to placebo ($p<0.0001$) -GAS scores over time for fluoxetine group vs. placebo group were significant ($p=0.02$)

Simpson, Yen, Costello, Rosen, Begin, Pistorello and Pearlstein, 2004.	25	Admitted women to the Women's Partial Program, a 5-day DBT-based partial hospital program.	20 women admitted to the Women's Partial Program, recruited using a brief self-report questionnaire. Sex-20 women, 0 men Mean age-34.84 Participants also had to meet 1 borderline personality disorder criterion pertaining to affective instability (e.g. lability or anger) & 1 pertaining to impulsivity. Exclusions: primary diagnosis of substance dependence, a seizure disorder, unstable medical conditions, a lifetime history of schizophrenia or bipolar disorder, monoamine oxidase inhibitor treatment in the prior 2 weeks or a previous adequate trial of fluoxetine; women who were pregnant, lactating or unwilling to use effective birth control.	All subjects received individual and group DBT. Fluoxetine (or placebo) was began at 20mg/day and dose advanced to max. anticipated dose of 40mg/day.	Measurements: -Assessment battery administered prior to treatment and at week 10. Included self-report instruments: Beck Depression Inventory (BDI), State –Trait Anxiety Inventory (STAI), Overt Aggression Scale -Modified (OAS-M), Dissociative Experiences Scale (DES), and the State-Trait Anger Expression Inventory (STAXI). A Global Assessment of Functioning scale (GAF) was also administered. Results: -No significant differences in scores from pre to post-treatment on all measures. -Within the DBT/placebo group, significant pre/posttreatment differences in BDI ($p<0.001$) and GAF ($p<0.001$) -No significant differences pre/posttreatment found Between DBT/fluoxetine group

Zanarini, Frankenburg, 2001	28	Women between the ages of 18 to 40 disturbed by moodines	Women between the ages of 18 &40 with diagnosis of BPD (per DSM-IV criteria) who	Half a tablet per day of study medication (each tablet contained either 2.5mg of olanzapine or matching placebo) at the start of the study. Dose was adjusted according to perceived response & side-effects.	Measurements: -Self-report measures-Symptom Checklist-90(SCL-90), the Hamilton Depression Inventory (HDI), Dissociatives Experiences Scale (DES). -Observer rated scales- the Positive and Negative Syndrome Scale (PANSS), Global Assessment of Functioning scale (GAF).

		s, distrustfulness, impulsivity, painful & difficult relationships recruited through advertisements in Boston area newspapers. Volunteers	answered advertisements in Boston area newspapers relating to whether they were disturbed by moodiness, distrustfulness, impulsivity, painful & difficult relationships. Mean age - 26.7y Sex-28 women, 0 men Exclusions: h/o treatment with olanzapine, medically ill, seizure disorder, currently being prescribed any psychotropic medication that they though was helping to alleviate troublesome symptoms, were actively abusing alcohol or drugs, or were acutely suicidal (i.e. had a clear-cut & pressing intent to commit suicide in the near future); those who were pregnant,		Results: -Olanzapine vs. placebo group experienced more change on all the SCL-90 scales except depression. On the SCL-90 anxiety scale improvement was significant (p=0.002). -Due to small numbers of subjects, results of secondary Outcome measures (HDI, DES, PANSS & GAF) not reported -More side effects were experienced by the olanzapine than the Placebo group including minor sedation (Fisher exact test=0.704), constipation (Fisher exact test =0.072), weight gain (Fisher exact test=0.026)

			breastfeeding, planning to become pregnant or not using reliable forms of contraception.		
Zanarini, Frankenburg, Parachini, 2004	45	Women aged 18 to 40 years disturbed by moodiness, distrustfulness, impulsivity, painful & difficult relationships recruited through advertisements in Boston, Mass. area newspapers. Inclusion criteria: Met DSM-IV criteria for BPD using borderline module of the Diagnostic Interview for DSM-IV Personality	45 women meeting criteria for BPD from source population. Sex-45 women Exclusions: Successful treatment with fluoxetine or olanzapine, medically ill, seizure disorder, currently prescribed any psychotropic medication, actively abusing alcohol or drugs, acutely suicidal (i.e. had a clear-cut and pressing intent to commit suicide in the near future). Also excluded were those who were pregnant, breastfeeding, planning to become pregnant, or not using reliable forms	2 capsules at beginning of study. Fluoxetine group, 1 capsule contained 10mg of fluoxetine & other capsule contained placebo. Olanzapine group, 1 capsule contained 2.5mg of olanzapine & the other contained placebo. Olanzapine-fluoxetine (OFC) group, 1 capsule containing 10mg of fluoxetine and the other contained 2.5mg of olanzapine.	Measurements: Observer-rated measures were Montgomery-Asberg Depression rating Scale (MADRS), Modified Overt Aggression Scale (OAS-M). Results: -OFC group showed greater improvement over time than fluoxetine on MADRS and OAS-M ($p=0.017$ & $p<0.001$). -Olanzapine group showed greater improvement than fluoxetine group on both outcome measures ($p<0.0001$ and $p=0.0033$). -Those in the olanzapine group experienced more mild sedation than those in the fluoxetine or the OFC group ($p=0.0064$). -Mild akathisia and weight gain were equally likely among all three groups.

		Disorders (DIPD-IV).	of contraception were also excluded.		
Bogensc hutz, Numberg, 2004.	40	Patients with BPD recruited from the community and outpatient clinics at a university psychiatric hospital.	Medically stable women and men between the ages of 18 and 60 years with diagnosis of BPD, recruited from the community & outpatient clinics at a university psychiatric hospital. Participants required to be free of mood stabilizers, antipsychotics, benzodiazepines and antidepressants for at least 2 weeks. Women of childbearing potential were required to employ effective contraception. Sex-25women & 15 men Exclusion: Those meeting criteria for schizophrenia, schizoaffective disorder, bipolar	Study medication started at 2.5mg/day (of olanzapine or placebo). Dose increased by 2.5-5mg increments/wk. up to 10mg/day based on clinical efficacy. After 8 wks, if needed, dose could be increased by 2.5-5mg increments/wk. to max. dose of 20mg/day. If intolerable side effects, dose could be decreased in 2.5-5mg increments/ week.	Measurements: -9 DSM-IV BPD criteria each scored on a 1-to-7 Likert scale analogous to the Clinical Global Impressions scale modified for borderline personality disorder (CGI-BPD). -Standard CGI as secondary global outcome measure. -Impulsive aggression measure using the Overt Aggression Scale modified (OAS-M) and the Anger, Irritability, and Assault Questionnaire (AIAQ). -Depression and anger measured using the Hamilton Rating Scale for Depression (HAM-D)and the Hamilton Rating Scale for Anger (HAM-A). -SCL-90 as secondary self-report measure covering multiple domains of psychopathology. -Alcohol & drug use measured using Addiction Severity Index (ASI) completed monthly -Movement disorders assessed using Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale & Simpson-Angus Scale. Results: -Olanzapine found to be superior to placebo on the CGI-BPD at endpoint ($p<0.05$) -On the secondary global measure (single item Global Clinical Impressions scale) results were significant in the olanzapine group compared to the placebo group. -At 8 wks, significant improvement on HAM-D, HAM-A and AIAQ -Weight gain significantly greater in olanzapine group than placebo group ($p=0.027$)

			affective disorder, current major depressive episode, psychotic disorder due to substance or a general medical condition, or substance dependence that was not in full or partial remission. Those who were actively suicidal (i.e. any clinically significant suicidal attempts in past 6 months or any current suicidal intent or definite plan, not included were self-injurious behavior with minimal potential for serious harm ex. Superficial cutting or burning), pregnant, had significant neurological impairment.		
Soler, Pasual, Campins, Barrachin	60	Patients referred from clinical	60 subjects referred from clinical services who	Participants randomly assigned to receive dialectical behavior therapy plus olanzapine or dialectical behavior therapy plus placebo in a	Measurement: -Clinical scales including Hamilton Depression rating Scale for affective symptoms, Hamilton Anxiety Rating Scale for anxiety symptoms, Clinical Global Impression

a, Puigdemont, Alvarez, Perez, 2005.		services. Inclusion criteria-meeting DSM-IV diagnostic criteria for BPD as assessed by the Structured Clinical Interview for DSM-IV Axis II Disorders and the Revised Diagnostic Interview for Borderlines; age of 18-45 years; Clinical Global Impression (CGI) severity of illness score more than or equal to 4; not receiving psychotherapy; for female subjects, using medically accepted contraception.	met inclusion criteria and who completed selection phase. Mean age-26.95y Sex-52 women, 8 men	1:1 ratio. Treatment dose for olanzapine was flexible ranging from 5 to 20mg/day.	(CGI) severity of illness scale to evaluate overall performance. -Biweekly behavioral reports on subject's most dysfunctional behaviors: episodes of impulsivity/aggressive behavior, self-injuring behavior/ suicide attempts, visits to psychiatric emergency services. Results: Analysis done on an intention to treat basis. -DBT & olanzapine group showed grater reduction in Depressive symptoms according to Hamilton depression scale scores compared to the DBT& placebo group ($p=0.004$). -Significant decrease in clinical anxiety according to the Hamilton Anxiety rating Score for the olanzapine treated group compared with placebo ($p<0.02$). -Greater decrease in impulsivity/aggression in the olanzapine group compared to the placebo group ($p=0.03$) -Self-injuring behavior/suicide attempts decreased in olanzapine group but this was not significant ($p=0.08$) -Significant improvement in CGI in DBT/olanzapine compared to DBT/placebo group. -Olanzapine group experienced significantly more weight gain than placebo patients ($p<0.05$) -Olanzapine group experienced a significant increase in Cholesterol levels ($p<0.04$)

Table 2: Quality ratings for randomized controlled trials included in systematic review. Ratings on a scale of 0-3 or ó to +++ for bias (with ó representing 3 and +++ representing 0)

(I)Randomized controlled trials with fluoxetine

Study Authors, Year	*Study Population*	*Potential for selection Bias*	*Measurement Tool-equal, reliable, valid*	*Potential for confounders*	*Analysis*	*Outcome reported adequately*	*Overall Quality*
Salzman, Wolfson, Schatzberg, Looper, Henke, Albanese, Schwartz and Miyawaki, 1995	*2*	*++(1)*	*2*	*++(1)*	*2*	*3*	*11*
Simpson, Yen, Costello, Rosen, Begin, Pistorello and Pearlstein, 2004.	*3*	*+(2)*	*1*	*+(2)*	*2*	*3*	*13*

(II)Randomized controlled trials with olanzapine

Study Authors, Year	*Study Population*	*Potential for selection Bias*	*Measurement Tool*	*Potential for confounders*	*Analysis*	*Outcome*	*Overall Quality*
Zanarini, Frankenburg, 2001	*2*	*+++(0)*	*2*	*++(1)*	*2*	*2*	*9*
Zanarini, Frankenburg, Parachini, 2004	*2*	*++(1)*	*1*	*++(1)*	*2*	*3*	*10*
Bogenschutz, Numberg, 2004	*2*	*+++(0)*	*1*	*++(1)*	*2*	*2*	*8*
Soler, Pasual, Campins, Barrachina, Puigdemont Alvarez, Pérez, 2005	*2*	*+(2)*	*1*	*+(2)*	*2*	*3*	*12*