

Research report

Evidenced-based pharmacologic treatment of borderline personality disorder: A shift from SSRIs to anticonvulsants and atypical antipsychotics?

P. Francis Abraham^{a,*}, Joseph R. Calabrese^b

^a 6140 S Broadway, Lorain, OH 44053, USA

^b 11400 Euclid Ave, # 200, Cleveland, OH 44106, USA

Received 31 October 2006; received in revised form 24 January 2008; accepted 30 January 2008

Available online 4 March 2008

Abstract

Objective: The authors performed a review of double-blind, controlled studies of psychotropic drugs to evaluate the evidence base supporting their use in treatment of borderline personality disorder.

Methods: English language literature cited in Medline and published between 1970 and 2006 was searched using the following terms: *anticonvulsants, antidepressants, antipsychotics, anxiolytics, benzodiazepines, borderline personality disorder, lithium, medication, mood stabilizers, pharmacotherapy, and psychotropics*. Only reports of double-blind, randomized, controlled trials were included.

Results: Twenty eight double-blind, randomized, controlled trials were identified which included anticonvulsants, classical neuroleptics, the benzodiazepine alprazolam, lithium, monoamine oxidase inhibitors, the novel antipsychotic olanzapine, selective serotonin reuptake inhibitors, tricyclic antidepressants, and omega-3 fatty acids. All but three were placebo-controlled. With the exception of alprazolam and tricyclics, the data from these trials revealed evidence of improvements, although often circumscribed and variable. The novel antipsychotic olanzapine appeared to have the most empirical support for having a favorable effect on borderline personality disorder.

Conclusion: A growing body of data suggests that there are psychotropic agents which appear to be well tolerated, and which to varying degrees may be expected to ameliorate the domains of psychopathology associated with borderline personality disorder. The research literature, on which practice should be optimally based, appears to suggest a need for a shift from antidepressants to anticonvulsants and atypical antipsychotics.

© 2008 Elsevier B.V. All rights reserved.

Keywords: Borderline personality disorder; Controlled trials; Drugs

1. Introduction

The borderline personality disorder (BPD), which is widely understood as having significant phenomenolo-

gical similarity to, and comorbidity with the mood disorders, designates a nosologic construct well familiar to mental health professionals. It is regarded, often with trepidation, that patients befitting this categorization will be refractory to treatment, demanding of resources, and at high risk for acute or dangerous presentations. While such attitudes may be justifiable, these patients

* Corresponding author. Tel.: +1 440 233 7232.

E-mail address: pabraham@nordcenter.org (P.F. Abraham).

are still all too often encountered in all clinical settings. For while they comprise 2–3% of the total population, patients with borderline personality disorder have been estimated to represent 6% of primary care outpatients, 15% of psychiatric outpatients, and 25% of psychiatric inpatients (Gunderson, 2001).

Given the sheer numbers of such patients, their disproportionately large utilization of health care resources, and the often formidable complexity, morbidity, and mortality associated with their diagnosis, it will be posited that a survey of evidence-based approaches to managing patients with BPD addresses a major unmet clinical need. There are no current reviews that focus on randomized, controlled trials notwithstanding the existence of such in sound quantity within the extant literature. Accordingly, the intent of this review is to present, in an elementary and up to date fashion, the meaningful body of evidence derived from controlled studies which may guide the clinician in selecting pharmacological maneuvers for managing the facets of borderline personality disorder.

2. Methods

English language literature cited in Medline was searched by combining the following terms: anticonvulsants, antidepressants, antipsychotics, benzodiazepines, borderline personality disorder, emotionally unstable personality disorder, lithium, medication, mood stabilizers, pharmacotherapy, and psychotropics. Articles published between 1970 and January, 2006 were reviewed. Only reports of double-blind, randomized, controlled trials involving clinical contexts were included. Additional studies were located in the bibliographies of these publications and were included if they met inclusion criteria.

3. Results

3.1. Antidepressants

3.1.1. *Tranylcypromine*

Within a double-blind placebo-controlled multi-trial crossover study comparing four active medications (alprazolam, carbamazepine, trifluoperazine, and tranylcypromine), Cowdry and Gardner (1988) reported positive findings regarding tranylcypromine. Sixteen female subjects with BPD and histories significant for behavioral dyscontrol were originally included. Of 12 patients randomized to tranylcypromine, 10 met *a priori* criteria of adequate duration (3 weeks). Patients were asked to complete self-ratings on numerous

symptoms associated with borderline psychopathology in addition to being concurrently rated by blinded physicians. Significant improvements were found in self-ratings of depression, anxiety, and rejection sensitivity. Improvement was also observed on physician-rated measures of global pathology, depression, rejection sensitivity, and many of the other items. Tranylcypromine did not show a significant reduction of behavioral dyscontrol episodes.

3.1.2. *Phenelzine*

In a post hoc analysis Parsons et al. (1989) reported the data collected in a trial of phenelzine, imipramine, or placebo for atypical depression within which 40 subjects were identified to have BPD by DSM-III criteria. Among these, response rates were 89%, 31%, and 20% to phenelzine, imipramine, and placebo respectively. Responders were defined as having “very much improved” or “much improved” on the Clinical Global Impressions of Improvement scale (CGI-I).

Subsequently Soloff et al. (1993) reported findings from a 5-week, parallel design trial to compare the efficacy of phenelzine, haloperidol and placebo on BPD inpatients on several measures of psychopathology. Patients with any history of schizophrenia or mania were excluded although current or prior non-psychotic major depression was not an exclusion criterion. Of the 108 patients randomized, 92 completed at least 3 weeks of medication as required for inclusion in the data analysis. Within the 3 arms administering either phenelzine, haloperidol, or placebo, 11%, 17%, and 18%, respectively, dropped out earlier for various reasons. Results showed some improvement in all 3 groups in all of the domains assessed: global, anxiety/obsessive, psychotic, depressive, impulsive–aggressive, and specific borderline symptoms. Significant, between-group differences included the finding the haloperidol and phenelzine, but not placebo showed a significant reduction on the Buss–Durkee Hostility Inventory (BHDI). These findings should be interpreted in view of certain potential confounds. Most importantly, this was a highly comorbid group especially with current major depressive disorder. The authors cite that 71% “of the final 80 SADS (Schedule for Affective Disorders and Schizophrenia) records” had current major depression. This high comorbidity and significantly greater number of depressed subjects randomized to take haloperidol are clear potential confounding factors.

3.1.3. *Fluoxetine*

Salzman and colleagues published the first double-blind placebo-controlled study of SSRI treatment of BPD

in 1994. Thirteen subjects were randomized to fluoxetine and 9 were randomized to placebo in this 13 week trial. These outpatients were slightly impaired with baseline Global Assessment of Symptoms (GAS) scores in the seventies. Patients with co-existing Axis I pathology as determined by an interviewing clinician were excluded. Randomized conditions were applied after a 7-day single-blind placebo “run-in” for all the subjects. Dosing was initiated at 20 mg/day and titrated to a maximum of 60 mg/day. Assessments were done by independent observers through the use of the Hamilton Depression Scale (HAM-D), GAS, and a personality disorder rating scale created for this study. Self-ratings were conducted with the Profile of Mood States (POMS) and an adaption of the Overt Aggression Scale (OAS) modified for self rating. In a primary analysis, only the anger subscale of the POMS and the GAS yielded a statistical improvement over placebo. Because of “high placebo responsiveness” the authors subsequently decided to “refine the analyses by creating a measure of placebo responsiveness and using it as a covariate in a series of repeated measures analysis of covariance.” With this revised strategy, analysis revealed that improvements in anger and depression were significantly greater in fluoxetine recipients on most of the assessments although any improvements on the POMS were never greater than 20% over baseline. Also on all measures but the HAM-D, fluoxetine was superior to placebo in number of patients improved versus number not improved.

In 1995 Markovitz and colleagues published results from a 14 week, fixed dose trial utilizing fluoxetine up to 80 mg daily. Nine subjects were randomized to fluoxetine and 8 to placebo. Data analysis revealed significant improvement over the placebo group in all measures utilized (GAS, HAM-D, Hamilton Anxiety Scale [HAM-A], Beck Depression Inventory [BDI], and Hopkins Symptom Checklist-90 [H-SCL-90]). While this is the most globally and consistently positive trial involving fluoxetine, it must be interpreted in view of the high degree of SSRI-responsive comorbidity in its subjects. In particular it should be noted that 10 of the 17 subjects were in a current episode of major depression. Also, 9 had generalized anxiety disorder, 6 had obsessive–compulsive disorder, 4 had panic disorder, and 12 had premenstrual syndrome.

Coccaro and Kavoussi (1997) carried out a 12 week study of fluoxetine for evaluating anti-aggressive efficacy using 40 personality disordered patients who did not have bipolar disorder, schizophrenia, or current major depression. Of these, 13 had BPD. While specific findings within the subset of borderline patients were not reported, fluoxetine but not placebo was associated

with an improvement in the CGI-I and the irritability and aggression subscales of the Modified Overt Aggression Scale (M-OAS) among all of the subjects. The improvements tended to occur most consistently at the end of the second month of the trial. There was no statistically significant improvement on secondary measures of depression with fluoxetine. Twelve of the sixteen patients who dropped out prior to completion of this trial were taking fluoxetine.

The most recent trial of an SSRI was designed to examine the effect of fluoxetine added to dialectical behavioral therapy (DBT) for the treatment of borderline personality disorder. Simpson et al. (2005) randomly assigned 9 out of 20 subjects who were receiving DBT to fluoxetine and 11 to placebo after a 1 week placebo wash-out period during which all other psychotropics were discontinued. Baseline pathology was substantial as evidenced by a mean Beck Depression Inventory score of 32 and the mean Global Assessment of Functioning (GAF) score in the high 40's. At the end of the 12-week trial, fluoxetine did not surpass placebo on any of the measures.

3.1.4. Fluvoxamine

Using ‘rapid mood shifts’, ‘impulsivity’, and ‘aggression’ — three subscales from the Borderline Personality Severity Index — as primary outcome measures, Rinne et al. (2002) examined the treatment responses of 38 “nonschizophrenic, nonbipolar” female patients with borderline personality disorder to placebo or fluvoxamine. Approximately one-third of these had comorbid anxiety or depressive disorders. Dosing was standardized to target 150–200 mg daily. Subjects were randomized to fluvoxamine or placebo for 6 weeks. Subsequently, placebo treated patients were administered with fluvoxamine for an additional 6 weeks. It was found that fluvoxamine conferred more improvement than placebo on rapid mood shifts but not on the impulsivity or aggression subscales.

3.1.5. Amitriptyline

After publishing a series of interim reports between 1986 and 1988, Soloff et al. 1989 described their final findings and impressions from a trial which ultimately was comprised of 90 inpatient borderline subjects (Soloff et al., 1986a,b, 1987, 1988, 1989). The investigators randomized substantially ill borderline subjects, some with active syndromal major depression, to haloperidol, amitriptyline, or placebo arms. The trial was for 5 weeks with the randomized study medication given after a period of at least 1 week of abstinence from prior medications. A multitude of ratings was utilized including the HAM-D,

Inpatient Multidimensional Psychiatric Scale (IMPS), Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI), Buss–Durkee Hostility Inventory (BDHI), and GAS. The average daily doses of haloperidol and amitriptyline were approximately 4.8 mg and 149 mg respectively at endpoint. Three patients receiving haloperidol, one receiving amitriptyline, and one receiving placebo terminated the trial before completing the minimum 2 weeks of drug exposure posited as necessary for inclusion in the analysis. All of the groups showed some improvements over time within certain categories of symptoms. On measures of “anxiety/hostility” both amitriptyline and haloperidol showed improvements over time on self-rated and observer-rated assessments (BDHI and IMPS components) in contrast to placebo. Haloperidol however was superior to amitriptyline for hostility on self-rated and observer-rated instruments. Haloperidol alone showed improvement over placebo on the SCL-90 measure of obsessive–compulsiveness. Only haloperidol treatment resulted in improvements in actual impulsive behaviors as rated with the Ward Scale of Impulse Action Patterns. Haloperidol was superior to placebo on all major measures of cognitive/schizotypal phenomena while amitriptyline was not. Haloperidol also significantly surpassed amitriptyline on each direct comparison in this area. Both haloperidol and amitriptyline were associated with greater improvements compared to placebo on self and observer-rated measures of depression (BDI and HAM-D 24). Still haloperidol was effective on more scores within the depressive spectrum than amitriptyline. Haloperidol and not amitriptyline was better than placebo on assessments of interpersonal sensitivity. Finally, only haloperidol showed superiority to placebo on measures of global functioning (GAS and SCL-90 general severity index).

Again it should be noted that this study allowed patients currently in a non-psychotic major depression, while excluding patients with mania or schizophrenia. This presumably substantive issue is only briefly addressed by the authors noting that “Response to amitriptyline [30% improvement on HAM-D score] was independent of a comorbid diagnosis of [current] major depression in borderline patients” (Soloff et al., 1989).

In summarizing these complicated findings, one is left with an impression that haloperidol had a broad spectrum of acute efficacy for substantially ill, inpatient borderline patients while amitriptyline, which may have been beneficial in some domains, was less effective than haloperidol, had no advantage even for depressive symptoms, and may have worsened outcomes in some patients as an interim subgroup analysis by this group suggested (1987).

3.1.6. Desipramine

See under Lithium (Links et al., 1990).

3.1.7. Imipramine

See under Phenelzine (Parsons et al., 1989).

3.1.8. Mianserin

In a six month trial designed to assess for differences in effect on suicidal behavior, Montgomery and Montgomery (1982) used 30 mg of mianserin or placebo in a group consisting of 58 personality disordered persons with DSM-III diagnoses of “mainly borderline or histrionic” disorders and who had multiple prior episodes of suicidal behavior but were without depression, schizophrenia, or “organic disease”. Thirty of 38 completers had BPD. There was no significant difference between the mianserin and placebo treated groups on the number of patients who carried out suicidal behaviors.

3.2. Classical neuroleptics

3.2.1. Haloperidol

See under Amitriptyline (Soloff et al., 1989), Phenelzine (Parsons et al., 1989), and Thiothixene (Serban and Siegel, 1984).

3.2.2. Thiothixene

“Low dose” thiothixene was compared to placebo among 50 patients with borderline and schizotypal personality disorders in a study by Goldberg et al. (1986). The average daily dose by the end of this twelve-week study was 8.7 mg. The investigators reported that regardless of whether diagnosed borderline or schizotypal, the patients randomized to thiothixene were more improved compared to placebo on physician-rated measures of illusions, ideas of reference, and psychoticism. Thiothixene was also superior on HSCL-90 scales of obsessive–compulsive symptoms and phobic anxiety. There were no differences on the HSCL-90 scale for depression or GAS.

Serban and Siegel (1984) published another study on a group of 52 outpatients with borderline and/or schizotypal personality disorders who were followed up for 3 months. Without the use of a placebo control, patients were randomized in a parallel, double-blinded design to either thiothixene or haloperidol. Dosing was flexible and conducted at weekly assessments by investigating physicians. Most patients reached a steady dosage by week 4. Resulting average daily dosages were 9.4 mg for thiothixene and 3 mg for haloperidol. Both groups showed significant improvement on the HAM-D

and in anxiety and derealization on another assessment. The thiothixene group was associated with significantly more improvement on depression, paranoia, and “general symptoms” on this latter (unspecified) assessment. Also, among the patients with BPD ($n=32$), thiothixene and not haloperidol was associated with a significant improvement from baseline on self-rated borderline symptoms.

3.2.3. Trifluoperazine

In their four-drug, placebo-controlled crossover trial Cowdry and Gardner (1988), included trifluoperazine among the active agents they studied. At an average dose of 7.8 mg daily, patients did show improvements on physician ratings of anxiety and suicidality. Three of the 10 randomized patients were terminated early by study doctors due to side effects.

3.2.4. Loxapine and chlorpromazine

A double-blind study comparing “low dose” loxapine and chlorpromazine in 80 outpatients with borderline personality was published by Leone (1982). With forty patients in each arm, clinician-rated, nurse-rated, and self-rated assessments were collected. The respective average daily doses for loxapine and chlorpromazine were 14.5 mg and 110 mg. Leone reported that during the 6-week trial patients in both groups showed significant improvement from baseline. While both drug groups improved, loxapine was associated with some significantly greater improvement than chlorpromazine at certain, mostly early, time points. The absence of a placebo arm and the intermittent character of differences among the two active groups diminish the interpretability of these findings.

3.2.5. Flupenthixol decanoate

Montgomery and Montgomery (1982) reported another 6-month study comparing historically suicidal personality disordered patients who were either administered flupenthixol decanoate 20 mg intramuscularly every 4 weeks or were likewise administered placebo in a 1:1 ratio. Twenty-three of the 30 completers were diagnosed specifically with BPD. By the fourth month of treatment and through the remainder of the study the number of suicide attempts was statistically lower in the active treatment group (3 out of 14 versus 12 out of 16). Benefits specifically to patients with borderline personality disorder were not reported.

3.3. Lithium

“Emotionally unstable character disorder” (EUCD) appears to have been a progenitor of borderline

personality disorder in early psychiatric taxonomic systems which was discarded in DSM-II. On this basis, Rifkin et al.’s (1972) placebo-controlled study of lithium carbonate in EUCD will be included in this review. In a crossover design, subjects were randomly assigned to receive either lithium or placebo first for 6 weeks followed by another 6 week trial with the other agent. Twenty one inpatients were included in the analysis. Lithium was well tolerated as dosed to a therapeutic level. The impressions of the blinded evaluators included more patients ($n=14$) being globally better during treatment with lithium. Patients taking lithium also had significantly less daily “extreme mood lability”.

More recently, Links et al. (1990) also found positive results in their randomly ordered crossover trials of lithium, desipramine, and placebo. Seventeen patients were assigned to the three agents in randomly consecutive order. Each trial lasted 6 weeks and was followed by a two week wash-out period. Outcome was assessed through use of the HAM-D, the Carroll Scale of Depression (CSD), selected parts of the Schedule for Affective Disorders and Schizophrenia-Change (SADS-change), overall patient perceptions, and overall (blinded) therapist perceptions. Chloral hydrate and nitrazepam as needed for sleep were the only concurrent psychotropics allowed during these trials. Three of the subjects met criteria for comorbid generalized anxiety disorder, 2 for panic disorder, and 1 for major depression. Average daily doses for lithium and desipramine were 985.7 mg and 162.5 mg respectively. Number of premature discontinuations was similar with both active medications. The only significant benefit found was that of lithium over placebo in therapists’ perceptions of improvement expressed by whether they would continue any treatment in the patient after the trial.

3.4. Anticonvulsants

3.4.1. Divalproex

Hollander et al. (2001) carried out the first randomized clinical trial with this compound. Sixteen patients were originally randomized. However, 10 dropped out prior to completion. All of the placebo group patients dropped out ($n=4$) as did 6 of the 12 in the divalproex group. None of the early terminations occurred due to side effects but rather due to lack of efficacy or “impulsive decisions”. Five of the six completers were considered to be responders as defined by a CGI-I score of 1 or 2 at endpoint. Their GAS and CGI-I scores were both statistically improved from baseline.

Female borderline patients who also had bipolar II disorder were studied with divalproex by Frankenburg

and Zanarini (2002). After the exclusion of patients with current major depressive or hypomanic episodes, 20 subjects were randomly assigned to divalproex and 10 to placebo. At the end of the 6 month trial, using last observations carried forward in their analyses, the investigators found that divalproex was superior to placebo in reduction of interpersonal sensitivity and anger/hostility as rated with the SCL-90 and in reduction of overall aggression rated with the M-OAS. The SCL-90 measure of depression did not reveal a significant advantage of divalproex.

To evaluate the efficacy of divalproex versus placebo in the treatment of impulsive aggression, Hollander et al. (2003) studied 246 outpatients having an M-OAS score of greater than 15 who met DSM-IV criteria for either Post-Traumatic Stress Disorder (PTSD) ($n=34$), intermittent explosive disorder (IED) ($n=116$) or cluster B personality disorders ($n=96$). Approximately 52 of those with cluster B personality disorders had BPD. While the drop-out rate among all patients was 41%, at the end of the 12 week trial significant differences favoring divalproex were found in reduction of M-OAS scores in cluster B personality group whereas these were absent in the PTSD and IED groups or in the total cohort of patients. The evaluable data also showed a significant advantage of divalproex on CGI-Severity scores in the cluster B group across several time points including the last 4 assessments.

3.4.2. Carbamazepine

As a component of a double-blind crossover study including four different 6 week drug trials and a placebo trial, Cowdry and Gardner (1988) detected that, among the sixteen female borderline patients, all of whom who had histories of prominent behavioral dyscontrol and who were concurrently receiving psychological therapy, there was a “dramatic” and statistically significant reduction in ratings of behavioral dyscontrol during the carbamazepine trial. Also, ratings conducted by blinded physicians demonstrated statistically significant differences in impressions of global functioning, anxiety, anger, euphoria, impulsivity, and suicidality between the carbamazepine and placebo trials among the eleven patients who had completed at least 3 weeks of the trials.

However, in a more recent double-blind parallel placebo-controlled trial involving 20 hospitalized borderline patients for a mean duration of 30.9 days, investigators De la Fuente and Lotstra (1994) reported finding no significant positive effects from carbamazepine.

3.4.3. Topiramate

Topiramate was evaluated by Nickel et al. (2004) to determine its effect on aggression in women meeting

diagnostic criteria for borderline personality disorder. The twenty-nine subjects participating in this eight week trial were randomized to receive placebo or active compound tapered up to a target dose of 250 mg/day in an approximate 1:2 ratio. The self-reported changes on the anger subscales of the State Trait Anger Experience Inventory (STAXI) were queried to generate the primary outcome measures. The topiramate-treated group was observed to have significantly greater reductions in four out of the five STAXI anger subscales when compared with the placebo group.

Subsequently Nickel et al. (2005) published a report of another nearly identically conducted trial evaluating topiramate and aggression in 42 male borderline patients with similar results.

3.4.4. Lamotrigine

Lamotrigine was subjected to randomized, double-blind assessment by Tritt et al. (2005) who detected positive results, as in the topiramate trials, on aggression in 24 women with BPD.

3.5. Benzodiazepines

3.5.1. Alprazolam

Cowdry and Gardner (1988) included an alprazolam trial in their multi-drug, placebo-controlled design study. Alprazolam at a mean daily dose of 4.7 mg, showed increased subjects’ ratings of suicidality, increased frequency of severe behavioral dyscontrol, and no improvements.

3.6. Novel antipsychotics

3.6.1. Olanzapine

Olanzapine is the only agent in this class for which there have been randomized, controlled trials published thus far. The first of these, by Zanarini and Frankenburg (2001), was comprised of 28 female subjects with BPD, 19 of whom were randomly assigned to active drug with the remainder assigned to placebo. Outcome measures included self-reported ratings on the anxiety, depression, paranoia, anger/hostility, and interpersonal sensitivity scales from the Symptom Checklist-90 (SCL-90). The duration of treatment was 6 months. Data analysis revealed a statistically significant improvement with time with olanzapine in all of the scales rated except for that of depression. There were no serious adverse effects and weight gain was “modest”, although significantly greater in the olanzapine-treated group.

Bogenschutz and Nurnberg (2004) reported their findings on a twelve-week trial of olanzapine monotherapy

in 40 subject with BPD. Twenty patients were randomized into each arm (olanzapine or placebo). Dosing was adjusted to a range of 2.5–20 mg daily during the assessments done at weeks 2, 4, 8, and 12. Thirty-five patients remained at the first assessment at 2 weeks and 23 of the 40 completed all 12 weeks. Outcome measures included a CGI scale applied to each of the 9 DSM-IV diagnostic criteria for borderline personality disorder (CGI-BPD) in addition to an overall CGI rating. By week 4, a significant separation was detected on the total CGI-BPD and overall CGI scores between the two arms using last observation carried forward methodology. Weight gain, averaging 3.71 kg in patients receiving olanzapine, was significantly higher than with placebo. There were no unexpected clinically significant adverse events.

Forty five women with borderline personality disorder were randomized to receive either olanzapine, fluoxetine, or the olanzapine–fluoxetine combination (OFC) in an 8-week study conducted by Zhanarini and colleagues (2004). Dosing was flexibly implemented by an unblinded physician and by endpoint had reached an average of 3.3 mg, 15 mg, and 3.2 mg/12.7 mg for the olanzapine, fluoxetine, and OFC groups respectively. The primary outcome measures were the Montgomery–Asberg Depression Rating Scale (MADRS) and the Modified Overt Aggression Scale (M-OAS). All three groups showed some improvement on both measures. However olanzapine and OFC showed a significantly higher degree of improvement over time than fluoxetine on both measures. Also, and perhaps most notably, olanzapine appeared to be superior to OFC in treating depressive symptomatology. Weight gain and sedation were higher in the olanzapine and OFC groups than in the fluoxetine group. No serious movement disorders occurred. Of the 3 (7%) patients who exited before completing all 8 weeks, two were from the OFC group and one from the fluoxetine group.

Soler et al. (2005) published findings from another trial which involved borderline patients who were all receiving dialectical behavioral therapy. Sixty patients were randomized to receive either placebo or olanzapine in a 1:1 ratio while continuing psychotherapy and prior psychotropic medications at constant doses. The trial lasted for 12 weeks following an initial 4-week baseline phase. The average daily dose of olanzapine was 8.83 mg. While both groups showed improvement on most of the assessments done, the olanzapine-treated group showed significantly greater improvement in depression and anxiety as determined by using intent to treat analysis on the HAM-D and HAM-A. A greater reduction in reports of impulsive/aggressive behavior was also found with active drug. Patients treated with

olanzapine gained more weight averaging an increase of 2.74 kg and had greater cholesterol increases.

3.7. Miscellaneous

3.7.1. Omega-3 fatty acids

The omega-3 fatty acid, ethyl-eicosapentaenoic acid (E-EPA) was studied by Zhanarini and Frankenburg (2003) to compare efficacy at 8 weeks with placebo in 30 female subjects with moderately severe borderline personality disorder. Randomizing 20 women to E-EPA 1 g daily and 10 women to placebo, the authors found statistical superiority of E-EPA in reducing M-OAS and MADRS scores. No clinically significant drug-related adverse effects occurred and 90% of subjects completed.

4. Discussion and conclusions

As has been noted, a current, qualitative survey of pharmacological treatments for borderline personality disorder may engender a novel impression, divergent from conventional clinical practices, expert opinion, and theoretical pronouncements previously disseminated (Gunderson, 2001; APA, 2001; Markovitz, 1995). This being namely that, apart from the SSRIs, a novel antipsychotic emerges as an effective and the most studied pharmacological agent for the short-term management of borderline personality disorder.

In five trials randomizing 100 patients to olanzapine, uniformly positive findings were reported. While 100 subjects is a relatively small total, it constitutes the largest group studied among all of the drugs surveyed. By comparison, there were a total of 80 subjects who received haloperidol and 67 who received fluoxetine. While no single investigation of olanzapine detected superiority to the comparator in all symptom-categories, the general consistency of the positive findings (Zhanarini and Frankenburg, 2001; Bogenschutz and Nurnberg, 2004; Zhanarini et al., 2004; Soler et al., 2005), the broad improvements in specific measures of borderline symptoms in the two studies in which these were explicitly assayed (Zhanarini and Frankenburg, 2001; Bogenschutz and Nurnberg, 2004), the positive ratings evident in *both* subjective *and* observer-rated measures whenever these were reported, the significant, and heretofore elusive, improvement in depressive symptomatology in three of the four studies (Bogenschutz and Nurnberg, 2004; Zhanarini et al., 2004; Soler et al., 2005), and the one study which evinced the persistence of positive effects for 6 months (Zhanarini and Frankenburg, 2001), would support this impression. Olanzapine appeared well tolerated with a total of 6

patients discontinuing its trials due to drug-related adverse effects. Not surprisingly, it was however associated with a mean weight gain of approximately 3 kg. Consequently, adherence to current consensus guidelines for monitoring metabolic parameters may be imperative with this agent (ADA et al., 2004). Particular caution may also be warranted with regard to potential complications in comorbid eating disorders in BPD populations. Also, although no greater risk of movement disorders was associated with olanzapine in these trials, it has elsewhere clearly demonstrated having this liability.

(Although an express departure from the methodology articulated at the outset of this review, it will be incidentally mentioned that there has been a recent, large ($n=451$), as of yet unpublished, trial of olanzapine in BPD (Zanarini et al., 2006) which has yielded similarly positive findings).

Moreover, while the SSRIs have heretofore been widely appraised as the pharmacological treatment of choice for borderline personality disorder (Gunderson, 2001; APA, 2001), this may need to be re-evaluated. While these drugs presumably are favored due to their perceived safety, the SSRIs cannot be assumed to be without dangers in this population (Teicher et al., 1990). There are six studies of these agents. Five of these trials involve fluoxetine (Zanarini et al., 2004; Salzman et al., 1994; Markovitz, 1995; Coccaro and Kavoussi, 1997; Simpson et al., 2005) and one trial studies fluvoxamine (Rinne et al., 2002). The fluoxetine trials reveal modest benefits largely limited only to the spheres of impulsive aggression and/or hostility. Of the two trials which have identified global improvements, Coccaro and Kavoussi (1997) and Markovitz (1995), the substantial (60%) drop-out rates among fluoxetine recipients in the Coccaro trial and the abundant fluoxetine-responsive comorbidities in the Markovitz trial must be acknowledged as potentially magnificent confounds. It is also important to note that this last study, one overtly and richly populated with subjects having current SSRI-responsive disorders, is the only one of the SSRI studies in which primary analysis detected a significant benefit within the realms of anxiety and depression. The results of Zanarini et al.'s (2004) direct comparison of olanzapine–fluoxetine combined (OFC), fluoxetine alone, and olanzapine alone are of particular interest. While there was no placebo group, and patients in all arms seemed to improve, both olanzapine and OFC were superior to fluoxetine alone. In addition, and perhaps most remarkably, olanzapine was superior to OFC in the treatment of *depressive symptoms*. Lastly, the most recent fluoxetine trial conducted (Simpson et al., 2005) detected no difference versus placebo. The single study of fluvoxamine found benefit in no area but “rapid mood shifts” (Rinne et al., 2002).

Despite their limitations and confounding variables, the three trials involving MAOIs are largely positive. It may be reasonable to conclude that until more definitive data are generated, MAOIs should not be excluded from consideration in the evidence-based pharmacotherapy of BPD. Conversely, every study involving a tricyclic implicated it as being inferior to the comparator, lacking in efficacy, and/or associated with exacerbation of pathology, (Parsons et al., 1989; Soloff et al., 1986b, 1987, 1988, 1989; Links et al., 1990) thereby making this class of drugs seem much less desirable. Conventional antipsychotics, certain anticonvulsants, and lithium may be of benefit in BPD, although the degree of their utility remains to be clarified. Albeit speculatively, collectively these data may be interpreted to convey provocatively similar patterns of pharmacological response among patients with BPD and those with bipolar mood disorders.

Among the several limitations which can be cited within the present discussion the following will be made explicit. First of all, the power of each individual trial was quite low. The largest investigation involved only 108 randomized subjects (Soloff et al., 1993). Also, and perhaps most critically, this review did not undertake meta-analytic methods such as comparison of effect sizes, numbers needed to treat/harm, or statistical quality assessments for the individual trials. A thorough review including the aforementioned methods based on data extracted before October, 2002 has been issued (Binks et al., 2006). It is clear that similar, quantitative assays of trials including the more recent olanzapine studies would be most needful along with the conduction of further, larger, well-designed studies of the issues proposed at the outset of this discussion. It may be hoped that the implementation of such investigations will lead to identification of factors which ultimately may be translatable into meaningful improvements in quality of life for borderline personality disorder patients. We submit that the need for such will scarcely be disputed among researchers, clinicians, and sufferers of this illness.

Role of funding source

Nothing declared.

Conflict of interest

No conflict declared.

Acknowledgement

I am hereby granting transfer of copyright to the publishers of The Journal of Affective Disorders if this manuscript is accepted for publication.

References

- American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity, 2004. Consensus development conference on antipsychotic drugs on obesity and diabetes. *J. Clin. Psychiatry* 65, 267–272.
- American Psychiatric Association, Practice Guideline for the Treatment of Patients with Borderline Personality Disorder, 2001. *Am. J. Psychiatry* 158, 10 (Oct suppl.).
- Binks, C.A., Fenton, M., McCarthy, L., Lee, T., Adams, C.E., Duggan, C., 2006. Pharmacological interventions for people with borderline personality disorder. *Cochrane Database Syst. Rev.* 25 (1), CD005653.
- Bogenschutz, M.P., Nurnberg, H.G., 2004. Olanzapine versus placebo in the treatment of borderline personality disorder. *J. Clin. Psychiatry* 65, 104–109.
- Coccaro, E.F., Kavoussi, R.J., 1997. Fluoxetine and impulsive aggressive behavior in personality disordered subjects. *Arch. Gen. Psychiatry* 54, 1081–1088.
- Cowdry, R.W., Gardner, D.L., 1988. Pharmacotherapy of borderline personality disorder: alprazolam, carbamazepine, trifluoperazine, and tranlycypromine. *Arch. Gen. Psychiatry* 45, 111–119.
- De la Fuente, J., Lotstra, F., 1994. A trial of carbamazepine in borderline personality disorder. *Eur. Neuropsychopharmacol.* 4, 479–486.
- Frankenburg, F.R., Zanarini, M.C., 2002. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind, placebo-controlled pilot study. *J. Clin. Psychiatry* 63, 443–446.
- Goldberg, S., Schultz, C., Schultz, P., Resnick, R., Hamer, R., Friedel, R., 1986. Borderline and schizotypal personality disorder treated with low-dose thiothixene vs. placebo. *Arch. Gen. Psychiatry* 43, 680–686.
- Gunderson, J.G., 2001. *Borderline Personality Disorder—A Clinical Guide*. American Psychiatric Press, Washington, DC.
- Hollander, E., Allen, A., Lopez, R.P., Bienstock, C., Grossman, R., Siever, L., Margolin, L., Stein, D., 2001. A preliminary double-blind, placebo-controlled trial of divalproex sodium in borderline personality disorder. *J. Clin. Psychiatry* 62, 199–203.
- Hollander, E., Tracy, K.A., Swann, A.C., Coccaro, E.F., McElroy, S.L., Wozniak, P., Somerville, K.W., Nemeroff, C.B., 2003. Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* 28, 1186–1197.
- Leone, N., 1982. Response of borderline patients to loxapine and chlorpromazine. *J. Clin. Psychiatry* 43, 148–150.
- Links, P., Steiner, M., Boiago, I., Irwin, D., 1990. Lithium therapy for borderline patients: preliminary findings. *J. Pers. Disord.* 4, 173–181.
- Markovitz, P., 1995. Pharmacotherapy of impulsivity, aggression, and related disorders. In: Hollander, E., Stein, D.J. (Eds.), *Impulsivity and Aggression*. John Wiley and Sons, New York, NY, pp. 263–287.
- Montgomery, S.A., Montgomery, D., 1982. Pharmacological prevention of suicidal behavior. *J. Affect. Disord.* 4, 291–298.
- Nickel, M.K., Nickel, C., Mitterlehner, F.O., Tritt, K., Lahmann, C., Leiberich, P.K., Rother, W.K., Loew, T.H., 2004. Topiramate treatment of aggression in female borderline personality disorder patients: a double blind placebo controlled study. *J. Clin. Psychiatry* 65, 1515–1519.
- Nickel, M.K., Nickel, C., Kaplan, P., Lahmann, C., Muhlbacher, M., Tritt, K., Krawczyk, J., Leiberich, P.K., Rother, W.K., Loew, T.H., 2005. Treatment of aggression with topiramate in male borderline patients: a double-blind, placebo-controlled study. *Biol. Psychiatry* 57, 495–499.
- Parsons, B., Quitkin, F.M., McGrath, P.J., Stewart, J.W., Tricamo, E., Ocepek-Welikson, K., Harrison, W., Rabkin, J.G., Wager, S.G., Nunes, E., 1989. Phenelzine, imipramine, and placebo in borderline patients meeting criteria for atypical depression. *Psychopharmacol. Bull.* 25, 524–534.
- Rifkin, A., Levitan, S.J., Galewski, J., Klein, D.F., 1972. Emotionally unstable character disorder—a follow-up study, I: description of patients and outcome. *Biol. Psychiatry* 4, 65–79.
- Rinne, T., van den Brink, W., Wouters, L., van Dyck, R., 2002. SSRI treatment of borderline personality disorder: a randomized, placebo-controlled clinical trial for female patients with borderline personality disorder. *Am. J. Psychiatry* 159, 2048–2054.
- Salzman, C., Wolfson, A.N., Schatzberg, A., Looper, J., Henke, R., Albanese, M., Schwartz, J., Miyawaki, E., 1994. Effect of fluoxetine on anger in symptomatic volunteers with borderline personality disorder. *J. Clin. Psychopharmacol.* 15, 23–29.
- Serban, G., Siegel, S., 1984. Response of schizotypal and borderline patients to small doses of thiothixene and haloperidol. *Am. J. Psychiatry* 141, 1455–1458.
- Simpson, E.B., Yen, S., Costello, E., Rosen, K., Begin, A., Pistorello, J., Pearlstein, T., 2005. Combined dialectical behavior therapy and fluoxetine in the treatment of borderline personality disorder. *J. Clin. Psychiatry* 65, 379–385.
- Soler, J., Pascual, J.C., Campins, J., Barrachina, J., Puigdemont, D., Alvarez, E., Perez, V., 2005. Double-blind, placebo-controlled study of dialectic behavior therapy plus olanzapine for borderline personality disorder. *Am. J. Psychiatry* 162, 1221–1224.
- Soloff, P.H., George, A., Nathan, S., Schulz, P.M., Ulrich, R.F., Perel, J.M., 1986a. Amitriptyline and haloperidol in unstable and schizotypal borderline disorders. *Psychopharmacol. Bull.* 22, 177–182.
- Soloff, P.H., George, A., Nathan, S., Schulz, P.M., Ulrich, R.F., Perel, J.M., 1986b. Progress in Pharmacotherapy of Borderline Disorders. A double blind study of amitriptyline, haloperidol, and placebo. *Arch. Gen. Psychiatry* 43, 691–697.
- Soloff, P.H., George, A., Nathan, R.S., Schultz, P.M., Perel, J.M., 1987. Behavioral dyscontrol in borderline patients treated with amitriptyline. *Psychopharmacol. Bull.* 23, 177–181.
- Soloff, P.H., George, A., Nathan, S., Schulz, P., Cornelius, J., 1988. Patterns of response to amitriptyline and haloperidol among borderline patients. *Psychopharmacol. Bull.* 24, 264–268.
- Soloff, P.H., George, A., Nathan, R.S., Schulz, P.M., Cornelius, J.R., Herring, J., Perel, J.M., 1989. Amitriptyline versus haloperidol in borderlines: final outcomes and predictors of response. *J. Clin. Psychopharmacol.* 9, 238–246.
- Soloff, P.H., Cornelius, J., George, A., Nathan, S., Perel, J.M., Ulrich, R.F., 1993. Efficacy of phenelzine and haloperidol. *Arch. Gen. Psychiatry* 50, 377–385.
- Teicher, M.H., Glod, C.A., Cole, J.O., 1990. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am. J. Psychiatry* 147, 207–210.
- Tritt, K., Nickel, C., Lahmann, C., Leiberich, P.K., Rother, W.K., Loew, T.H., Nickel, M.K., 2005. Lamotrigine treatment of aggression in female borderlines: a randomized, double-blind, placebo-controlled study. *J. Psychopharmacol.* 19, 287–291.
- Zanarini, M.C., Frankenburg, F.R., 2001. Olanzapine treatment of female borderline personality disorder patients: a double blind placebo-controlled pilot study. *J. Clin. Psychiatry* 62, 849–854.
- Zanarini, M.C., Frankenburg, F.R., 2003. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am. J. Psychiatry* 160, 167–169.

Zanarini, M.C., Frankenburg, F.R., Parachini, E.A., 2004. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine–fluoxetine combination in women with borderline personality disorder. *J. Clin. Psychiatry* 65, 903–907.

Zanarini, M.C., Schultz, S.C., Detke, H.C., Tanaka, Y., Zhao, F., Lin, D., DeBerdt, W., Corya, S., 2006. A dose comparison of olanzapine for

the treatment of borderline personality disorder: a 12-week randomized, double-blind, placebo-controlled study. 25th Biennial Congress of the Collegium Internationale Neuro-Psychopharmacologium; July 2006. Chicago, IL.