PHARMACOTHERAPY AND BPD

DIMEFF, L.A., MCDAVID, J., & LINEHAN, M.M.(1999)

Double-Blind Pharmacotherapy Outcome Studies Using BPD Samples

Study	Medications	Design	Outcomes & Comments
1. Leone, 1982.	chlorpromazine (M=110 mg/d) and loxapine (M=14.5 mg/d).	Double-blind randomized six-week acute treatment trial with BPD outpatients (n=80). Each condition included 24 female and 16 male Ss. No placebo-control condition was used. The assessment battery focused almost exclusively on measurement of affective dysregulation, including anxiety, depressed mood, and hostility, with very limited assessment of cognitive dysregulation (only confusion was assessed using the Profile of Moods Scale).	Eleven of the total N (13.8%) failed to complete at least three weeks of the trial. Both medications resulted in statistically significant improvements compared to baseline scores thorughout the evaulation. Ss using loxapine were significantly more improved on anxiety and depressed mood at Week 1 and Week 2 as measured by the Brief Psychiatric Rating Scale (BPRS) and systematic nursing observations. Differences between medication conditions disappeared by Week 4. One statistically significant finding -- reduction in depressed mood on the BPRS-- was observe at the post-treatment follow-up assessessment favoring loxapine.
2. Serban & Siegel, 1984.	haloperidol (M=3 mg/d ± 0.8 mg/d) and thiothixene (M= 9.4 mg/d ± 7.6 mg/d).	Double-blind, randomized trial of outpatients (n=52) meeting criteria for BPD, Schizotypal Personality Disorder (SPD) or both (35.6%). Ss were divided evenly between two active treatment conditions, each with 18 males and 8 females. No placebo-control condition was used.	Attrition information is scant. Ten Ss withdrew from the study within the first month due to side effects and/or inefficacy of the treatment. This group was apparently excluded from the intent to treat sample (n=52). Of the 52, 46 Ss (88%) remained in the study throughout the three-month trial. Eighty-four percent were markedly to moderately improved at the 3-month follow-up, with Ss responded more favorably to thiothixene than haloperidol in reducing general symptoms, anxiety, depression, and paranoia. Outcomes did not vary as a result of diagnoses. Over 80% of Ss in both conditions reported numerous adverse medication reactions. It is possible that that thiothixene's superior performance in this trial resulted from the failure to use a sufficient and equivilant dose of haloperidol.
3. Goldberg, Schulz, Schulz, Resnick, Hamer, & Friedel, 1986.	thiothixene (M= 8.7 mg/d; range, 2 mg to 35 mg).	Double-blind, placebo-controlled trial involving outpatients (n=50) meeting criteria for BPD and/or Schizotypal PD. About 40% met diagnostic criteria for both BPD and SPD. Ss selected on the basis of having ≤ 1 psychotic symptom. One week medication washout followed by random assignment to 12-week trial of thiothixene vs. placebo.	Only 45.8% of experimental Ss (11 of 24) completed the trial, compared to 57.8% Ss in placebo condition (15 of 26). Thiothixene significantly reduced illusions, ideals of reference, psychoticism, phobic anxiety, and obsessive-compulsivity in comparison to placebo. Near significant trends favoring thiothixene were observed on depersonalization-derealization, anger-hostility, and somatization. No differences were observed on pre/post depression scores. Ss with BPD-only has a significantly greater pre/post reduction in social phobia compared to Ss with SPD or both. No other differences as a result of diagnosis were observed.
4. Soloff, George, Nathan, Schulz, Ulrich, & Perel, 1986.	amitriptyline (M=147.62 mg/d; range, 100 mg to 175 mg) and haloperidol (M=7.24 mg/d; range, 4 mg to 16 mg).	Double-blind, placebo-controlled randomized trial in Ss diagnosed with BPD and/or SPD (n=64). Following one- week washout, 13 Ss no longer demonstrated ongoing symptom severity so were excluded from analysis. The intent to treat sample was restricted to Ss who had taken medications for two or more weeks (n=61).	Ss in all groups demonstrated statistically significant improvements over time, however the greatest gains occurred in the active medication conditions. Haloperidol was significantly superior to placebo and amitriptyline across a broad range of symptoms, including subjective complaints of hostility, paranoid or psychotic ideation, anxiety, phobic anxiety, obsessive-compulsive behaviors, and depressed mood and interpersonal sensitivity. Modest effects in the amitriptyline condition were limited to reductions in depression. Haloperidol had only a modest effect against schizotypal symptoms. Haloperidol was equivalent to amitriptyline in reducing depression. Ss with greatest response to haloperidol presented a sustained pattern of both affective and schizotypal symptoms. Magnitude of change was modest, but considered clinically and statistically significant.

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5. Cowdry & Gardner, 1988.	alprazolam (M= 4.7 mg/d), carbarmazepine (M= 820 mg/d), tranylcypromine (M= 40 mg/d), and trifluoperazine, (M= 7.8 mg/d).	Double-blind, placebo-controlled crossover trial in an outpatient setting while Ss also received psychotherapy. All Ss (n=16) were female and had BPD, as well as histories of severe dysphoric mood and behavioral dyscontrol but no current major depression. A full medication trial involved a two-week induction, four week maintenance with constant dosage, a week of medication taper, and at least one medication-free week before beginning next drug trial.	Differential completion rates were reported by condition, ranging from 38% (trifluoperazine) to 75% (tranycypromine). The most favorable outcomes were achieved with tranylcyromine which enhanced mood, reduced anxiety and impulsivity. Carbamazepine produced dramatic improvements, especially in decreasing the severity of behavioral dyscontrol, however severe melancholic depression developed in three Ss. Alprazolam significantly increased behavioral dyscontrol and suicidality ratings, but was regarded by patients as more beneficial than other agents. Patients having a favorable response to one medication were not likely to respond favorably to another medication..
6. Parsons, Quitkin, McGrath, Stewart, Tricamo, Ocepek-Welikson, Harrison, Rabkin, Wager, & Nunes, 1989.	imipramine, 300 mg. day max phenelzine, 90 mg max.	Double-blind, placebo-controlled trial of Ss with BPD and atypical depression but no other Axis I diagnosis. Part of a larger pharmacotherapy trial for atypical depression, 40 of the original sample (n=171) met 5 or more diagnostic criteria for BPD; 61 met 4 or more of the BPD criteria. Trial divided into two six-week phases; non-responders and Ss who responded to the placebo in the initial phase were removed from the second phase while responders received another six weeks of acute treatment. The second phase was intended to ensure that clinical gains persisted and were not transient.	Phenelzine was consistently superior to imipramine. Using the more stringent cut off for BPD (5 or more criteria), 20% of the original sample responded to the placebo, 38% to imipramine, and 89% to phenelzine. In the second trial, 19% responded favorably to the placebo, 42% to imipramine, and 100% to phenelzine. Results from this study demonstrated a strong relationship between the number of BPD symptoms and the efficacy of phenelzine. In patients having four or more BPD symptoms, 92% of phenelzine- and 35% of imipramine-treated patients were deemed "responders." In patients meeting fewer than four BPD criteria, there appeared little difference in efficacy between the two medications (65% of phenelzine-treated patients were judged as "responders" compared to 63% of the imipramine-treated patients).
7. Links, Steiner, Boiago, & Irwin, 1990.	desipramine (M= 162.5 mg/d) and lithium (M=985.7 mg/d).	Preliminary findings from a double-blind, random-order placebo-control crossover trial lasting 22 weeks comparable in to the Cowdry & Gardner (1988) crossover trial. Ss (n=19) met criteria for BPD; 18 were female and one was male; 42% had comorbid atypical depression. Of the 57 outpatient Ss referred to the study, 24 refused to participate in this trial.	Meaningful interpretation of this data and generalization is hampered by significant drop out rates. Two patients (11.8%) dropped out of treatment before taking any medication. Five dropped out after completing the first arm (29.4%). Only 58.8% of Ss completed two or more arms of the study. With few exceptions, no significant differences were found between lithium vs. placebo and desipramine vs. placebo using the Hamilton Depression Scale and Carroll Scale for Depression. While not statistically significant, eight of 11 Ss on lithium improved on measures of anger and suicidal symptoms (vs. four of 11 in the desipramine condition). The only statistically significant finding that emerged was on therapists' rating of improvement, favoring lithium.

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8. Markowitz, 1995	fluoxetine, maintenance dose = 80 mg/d.	Double-blind, placebo-controlled trial in Ss diagnosed with BPD (n=17). Acute treatment lasted 14 weeks. Primary measures included Hamilton Anxiety Scale (HAM-A), Hamilton Depression Scale (HAM-D), Beck Depression Inventory (BDI), and Global Assessment Scale (GAS).	This study was published as a non-peer reviewed chapter, but is the first published outcome data from a controlled clinical trial on the efficacy of SSRIs in Ss with BPD. The review of this study is very general and provides a very limited view of the specific findings. Seven of nine Ss in fluoxetine condition completed the entire trial, compared to seven of eight in the placebo condition. Statistically significant improvements favoring fluoxetine were found across all outcome measures. Ss receiving fluoxetine continued to demonstrate ongoing significant gains over time, suggesting that the 14-week trial may have been insufficient to capture the full extent of improvement able to be derived from its use. In open trials using fluoxetine, Markowitz and colleagues (1991) reported reductions in self-injury. No data is provided from this double-blind trial regarding self-injury or other impulsive behaviors.
9. Soloff, Cornelius, George, Nathan, Perel, & Ulrich, 1993.	haloperidol (M= 4 mg/d); phenelzine (M= 60 mg/d).	Double-blind, placebo-controlled randomized trial of consecutive admits with BPD to inpatient psychiatric hospital (n=108); 82 (75.9%) were female and 26 (24.1%) were male. One-week drug washout was followed by a five-week acute treatment phase. Patients with drug and/or alcohol deficits or dependence were excluded from this study. Replication study of prior Soloff et al. (1986) research.	Thirty-two Ss (30%) dropped out from the study. Three way comparisons between groups revealed superior efficacy of phenelzine, followed by placebo and haloperidol on measures of depression, borderline psychopathology, and anxiety. Pairwise comparisons between medication and placebo revealed significant efficacy of phenelzine to reduce anger and hostility; phenelzine was not efficacious in treating atypical depression or hysteroid dysphoria. Unable to replicate prior reports demonstrating efficacy of antipsychotics. Phenelzine dosage may have been insufficient, but patients were experiencing numerous side effects and were uncooperative about using higher dosage. Unable to replicate prior findings that demonstrated the efficacy of antipsychotics.
10. Cornelius, Soloff, George, Ulrich, & Perel, 1993; Cornelius, Soloff, Perel, & Ulrich, 1993.	haloperidol (≤ 6mg/d) and phenelzine(≤ 90 mg/d). Medication doses were generally unchanged from acute treatment trial.	Double-blind, placebo-controlled continuation study in 14 male and 40 female Ss with BPD (n=54). This 16 week trial followed a five-week acute therapy phase (see Soloff, et al., 1993). Eligibility for this trial was based on improvement obtained in the acute treatment phase as measured by a five or more point increase on the GAS and an absolute improvement over the criteria for initial inclusion. Of the 54 Ss, 14 were on haloperidol, 22 on phenelzine, and 18 on placebo.	The purpose of this continuation trial was to aid in determining how long to continue pharmacotherapy in patients who have stabilized with acute therapy. Attrition rates considerably high among haloperidol Ss (64%) within the first eight weeks, compared to 28% among placebo Ss. While haloperidol continued to be effective beyond the acute phase for irritability, Ss in this group had higher levels of depression, hypersomnia, and leaden paralysis. Phenelzine produced only modest effects beyond acute phase for depression and irritability; it was however activating.

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