# Phenylpropanolamine Appears Not to Promote Weight Loss in Patients With Schizophrenia Who Have Gained Weight During Clozapine Treatment

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***Background:*** Weight gain is a common side effect of clozapine treatment and may expose patients to obesity-associated health risks. We proposed that concomitant treatment with an appetite suppressant such as phenylpropanolamine (PPA) would lead to a decrease in appetite and therefore loss of weight.

***Method:*** This was a 12-week, double-blind, randomized, placebo-controlled trial of PPA, 75 mg/day, in outpatients with treatment-refractory schizophrenia (DSM-IV) who were stable on clozapine treatment for at least 4 months and had gained > 10% of their baseline body weight since starting clozapine. Patients were evaluated for adverse effects and weighed weekly. A Positive and Negative Syndrome Scale (PANSS) assessment, a short dietary quiz, and blood indices were completed monthly.

***Results:*** Sixteen patients were equally randomly assigned to receive PPA or placebo. The groups did not differ in mean age, baseline weight, dose of clozapine, baseline PANSS scores, or the percent of weight gained since the start of clozapine. There was no significant effect of treatment on weight ($t = 0.219$, $df = 10$, $p = .831$). There was no significant change in either the total PANSS scores ($t = –0.755$, $df = 10$, $p = .468$), the positive or negative symptom cluster scores, or any of the remaining variables.

***Conclusion:*** Phenylpropanolamine 75 mg/day was well tolerated but was not effective in reversing established weight gain associated with clozapine treatment in stable outpatients with schizophrenia.

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While chronic obesity is increasing across all groups in the United States, it is particularly prevalent among patients with schizophrenia.[1] Limited educational, nutritional, and recreational resources in combination with anergia and amotivation may predispose individuals with schizophrenia to obesity. Furthermore, antipsychotic drugs per se have also been implicated in weight gain. While some data suggest that patients receiving low-potency typical antipsychotics tend to gain more weight than those receiving high-potency drugs, weight gain is a particular concern during treatment with some of the atypical antipsychotics. For instance, clozapine use is associated with greater and more prevalent weight gain than any other antipsychotic drug.[2–7] Weight gain with olanzapine may be as great as with clozapine.[8] Risperidone appears to cause less weight gain compared with other atypical agents,[9] while the extent of quetiapine's effect on weight remains unclear.

Chronic obesity is associated with significant morbidity and mortality. The risk of developing diseases such as non–insulin dependent diabetes mellitus, coronary artery disease, hypertension, osteoarthritis, gall bladder disease, and even some cancers is increased in obese patients.[10] Furthermore, obesity may exacerbate concerns about self-esteem and lead to poor medication adherence. Ideally, weight gain associated with antipsychotic drugs should be detected in its early stages and treated effectively. Unfortunately, the standard regimen for achieving weight reduction, namely restriction of caloric intake in combination with behavior modification and exercise, is difficult to sustain in any population. Accordingly, a safe yet effective pharmacologic agent that promotes weight loss in patients with schizophrenia would be of considerable clinical value.

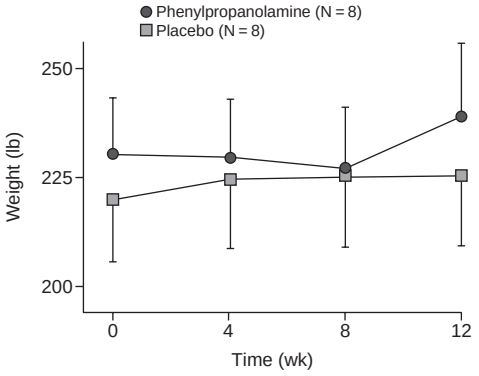
Until recently, the $\alpha_1$ agonist phenylpropanolamine (PPA) was sold over the counter in the United States as an appetite suppressant. (PPA was removed from the market due to concerns of hemorrhagic stroke.[11]) Its anorexiant actions are thought to be mediated by augmentation of noradrenergic transmission. PPA administered in doses of 75 mg/day to mildly obese but otherwise healthy individuals (10%–45% over ideal body weight) may promote

Table 1. Demographic Comparison Between Phenylpropanolamine (PPA)- and Placebo-Treated Groups[a]

| Demographic Factor | PPA (N = 8) | Placebo (N = 8) | p Value | t |
|---|---|---|---|---|
| Age, mean, y | 42.0 | 46.5 | .71 | 0.38 |
| Male/female, N | 8/0 | 6/2 | | |
| Clozapine dose, mean ± SD, mg/d | 506 ± 115 | 431 ± 187 | .35 | 0.97 |
| Baseline weight, mean ± SD, lb | 231 ± 35.5 | 220 ± 41.3 | .60 | –0.55 |
| Final weight, mean ± SD, lb | 234 ± 7.8 | 223 ± 5.4 | .83 | 0.22 |
| Baseline PANSS score, mean ± SD | 49.9 ± 9.9 | 51.6 ± 13.6 | .77 | –0.29 |
| Final PANSS score, mean ± SD | 45.5 ± 6.5 | 50.3 ± 7.4 | .47 | –0.76 |
| % Weight gain on clozapine treatment, mean ± SD | 30.1 ± 14.9 | 26.3 ± 17.7 | .66 | 0.46 |

[a]Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 1. Weight (mean ± SEM) of Study Participants Over 12 Weeks




modest weight loss (3.4%–8.0%).[12–15] Accordingly, we posited that PPA could be a useful adjunct for promoting weight loss in stable, antipsychotic drug–compliant patients with schizophrenia. Our primary hypothesis was that PPA treatment would lead to a significant weight reduction in obese patients who were stable and compliant with their clozapine treatment program. Our secondary hypothesis was that PPA would not affect symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS).

## METHOD

This was a randomized, double-blind, placebo-controlled 12-week study. It was approved by the Institutional Review Board of the Veterans Administration Medical Center (VAMC). Patients or legal guardians provided written consent. All subjects were recruited from a pool of outpatients in a clozapine treatment program administered in accordance with VAMC guidelines.[16] Patients met DSM-IV criteria for schizophrenia and were treatment intolerant or resistant[17] prior to initiation of clozapine treatment. The clozapine dose was determined clinically. Patients presented to the clozapine clinic weekly and participated in group education and group therapy. To be eligible for this study, patients had (1) to be on a stable dose of clozapine therapy for at least 4 months and (2) to experience a > 10% increase in body weight since starting clozapine treatment. Exclusion criteria included (1) objection from primary treating psychiatrist; (2) previous treatment with stimulants for weight loss; (3) uncontrolled hypertension, severe renal dysfunction, diabetes mellitus, or arrythmias; (4) pregnancy or lactation; and (5) psychiatric hospitalization or suicidal or homicidal ideation in the preceding 6 months.

Patients were randomly assigned to take either sustained-release PPA (Thompson Medical), 75 mg, or an identically appearing placebo with breakfast for a 12-week period. The study medication was dispensed in 7-day quantities, along with the weekly clozapine supply. Blood pressure, pulse, weight, and adverse events were recorded by clinic staff at baseline and weekly. Baseline assessments included the PANSS,[18] Abnormal Involuntary Movement Scale,[19] and Simpson-Angus Scale[20] as well as an electrocardiogram. The PANSS was repeated during weeks 4, 8, and 12. Serum glucose, glycosylated hemoglobin, and total cholesterol were drawn at baseline, 4, 8, and 12 weeks. All clozapine outpatients attended mandatory monthly dietary counseling. A 10-question dietary quiz was administered at each counseling session to reinforce important information. Adverse events were evaluated and recorded by the investigators during each weekly visit. Data were analyzed by analysis of variance with treatment as the main factor and time as the repeated factor. In addition, an a priori decision was made to compare initial and final indices by paired t tests.

## RESULTS

Sixteen patients were equally randomly assigned to receive either PPA or placebo. The groups did not differ in mean age, baseline weight, dose of clozapine, baseline PANSS scores, or the percent of weight gained since the start of clozapine treatment (Table 1). Four patients did not complete the study (2, PPA; 2, placebo). Reasons for withdrawal from the study included adverse reactions (diarrhea, nervousness, anxiety) and protocol noncompliance. There was no significant effect of treatment on weight ($t = 0.219$, $df = 10$, $p = .831$) (Figure 1; see Table 1). There appeared to be some slight weight loss in the PPA group from week 0 through week 8, but, by week 12, the groups were indistinguishable (Figure 1). There was no significant change in either the total PANSS scores ($t = –0.755$, $df = 10$, $p = .468$) or the positive and negative symptom cluster scores. Furthermore, there were no significant changes in any of the remaining variables.

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## DISCUSSION

Contrary to our primary hypothesis, in a 12-week, double-blind, placebo-controlled trial, PPA did not promote weight reduction in patients with schizophrenia who had previously gained weight during clozapine treatment. On the other hand, PPA did not affect symptoms of psychosis. Our results must be interpreted in terms of methodological limitations. This was intended as a pilot study and hence only 12 patients completed the study. We had determined that with a sample size of 6 in the PPA and placebo groups, the difference in weight change between the groups would have had to be at least 11 lb for detection with a power of 0.8.

We selected a PPA dose of 75 mg and study duration of 12 weeks in keeping with studies suggesting that phenylpropanolamine was an effective agent for weight loss in non–psychiatrically ill obese patients.[12–15] On the other hand, several of these studies differed from ours in that they combined PPA with caloric restriction, exercise, and behavior modification. Finally, we selected patients who had gained at least 10% of their body weight since the initiation of clozapine treatment. In other studies of pharmacologic adjuncts, weight loss is more prominent in those patients who are the most obese. Our patients would fall into the moderately obese spectrum. We did not monitor PPA levels in urine or serum. On the other hand, by virtue of being compliant with the clozapine treatment program the patients were self-selected for general compliance. All appeared to be motivated by a desire to lose weight.

Clozapine-associated weight gain is well recognized. Wiebe[2] originally reported that 5 clozapine-treated patients gained 17 to 50 lb over 1.5 to 16 months. A later review of 36 patients found a mean weight increase of 10.6% over a 6-month period.[6] Similarly, John et al.[7] noted that of 82 patients, 73% of them gained a mean of 11.55 ± 9 lb (range, 1–43 lb) after 3 months of clozapine therapy. In the first prospective study of weight gain, 21 clozapine-treated patients gained an average of 13.8 lb over the first 16 weeks of clozapine therapy.[4] The weight gain was not evenly distributed. Of those who gained weight, over half gained less than 10% of their baseline weight, whereas about 15% gained more than 20% of their baseline weight. Similar results were obtained in a larger sample of 82 patients,[5] in which weight gain persisted throughout the 24 weeks of the study. An alarming 50% of the patients increased their baseline weight by more than 20%. In a double-blind comparison of haloperidol (N = 20) and clozapine (N = 19), the clozapine-treated patients gained significantly more weight (7%) than the haloperidol group (1%) in the first 10 weeks.[4] Weight gain continued through a 1-year follow-up.[4] Indeed, continuing weight gain has been reported for up to 46 months after initiation.[21] Our design required clozapine treatment for at least 4 months. However, most patients had been receiving clozapine for over 18 months and therefore had established weight gain. Several investigators have noted an inverse relationship between weight gain and total Brief Psychiatric Rating Scale (BPRS) scores,[3,4,6] but this finding has not been consistently replicated.[5]

To date, there has been only 1 other prospective study of stimulant use to treat weight gain related to antipsychotic use.[22] Twenty-nine patients who were receiving either fluphenthixol or clopenthixol decanoate were randomly assigned to receive either dexfenfluramine 30 mg/day or placebo for 12 weeks. Mean weight loss in the dexfenfluramine group was 5.4 ± 3.4 kg versus 2.8 ± 1.65 kg in the placebo group. While no BPRS changes were noted, 6 patients in the dexfenfluramine group dropped out due to adverse events. In smaller pilot studies, fenfluramine was found to worsen either BPRS scores or neuropsychological function in patients with treatment-resistant schizophrenia.[23,24]

In our sample, PPA did not affect signs or symptoms of psychosis. There are case reports of psychosis related to PPA use for weight gain or decongestant purposes.[25,26] The patients involved often had underlying psychiatric illnesses, including schizophrenia and bipolar disorder, and PPA was taken with other stimulant drugs (caffeine, other decongestants).[27,28] There are also reports in which psychosis developed during combined use of PPA and drugs such as cocaine.[27,29] In making extrapolations about the safety of PPA in schizophrenia, it must be noted that our patients were all highly stable and compliant with clozapine treatment.

In summary, PPA treatment in conjunction with monthly nutritional counseling did not appear to promote weight loss in patients who had gained weight during clozapine treatment. The implications of our study are limited by the small sample and by the omission of more aggressive weight-reduction adjuncts (e.g., an exercise program). We also note that our sample consisted of patients who had already gained weight. Whether the institution of a rigorous education and exercise program in conjunction with an anorexic agent at the inception of clozapine treatment could prevent weight gain must be determined in future studies. Given the health risks of obesity and the increasing use of atypical antipsychotic drugs associated with significant weight gain, further investigations are merited.

*Drug names:* clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

## REFERENCES


1. Gopalaswamly AK, Morgan R. Too many chronic mentally ill disabled patients are too fat. Acta Psychiatr Scand 1985;72:254–258
2. Wiebe EJ. Weight gain with clozapine treatment [letter]. Can J Psychiatry 1993;38:70
3. Bustillo JR, Buchanan RW, Irish D, et al. Differential effect of clozapine on weight: a controlled study. Am J Psychiatry 1996;153:817–819
4. Leadbetter R, Shutty M, Pavalonis D, et al. Clozapine-induced weight gain: prevalence and clinical relevance. Am J Psychiatry 1992;149:68–72


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5. Umbricht DSG, Pollack S, Kane JM. Clozapine and weight gain. J Clin Psychiatry 1994;55(9, suppl B):157–160
6. Lamberti JS, Bellnier T, Schwarzkopf SB. Weight gain among schizophrenic patients treated with clozapine. Am J Psychiatry 1992;149: 689–690
7. John JP, Chengappa KN, Baker RW, et al. Assessment of changes in both weight and frequency of use of medications for the treatment of gastrointestinal symptoms among clozapine-treated patients. Ann Clin Psychiatry 1995;7:119–125
8. Gupta S, Droney T, Al-Samarrai S, et al. Olanzapine-induced weight gain [letter]. Ann Clin Psychiatry 1998;10:39
9. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(suppl 7):22–31
10. Atkinson RL, Hubbard VS. Report on the NIH Workshop on Pharmacologic Treatment of Obesity. Am J Clin Nutr 1994;60:153–156
11. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826–1832
12. Altschuler S, Frazer DL. Double-blind clinical evaluation of the anorectic activity of phenylpropanolamine hydrochloride drops and placebo drops in the treatment of exogenous obesity. Curr Ther Res 1986;40: 211–217
13. Greenway F. A double-blind clinical evaluation of the anorectic activity of phenylpropanolamine versus placebo. Clin Ther 1989;11:584–589
14. Weintraub M, Ginsberg G, Stein EC, et al. Phenylpropanolamine OROS (Acutrim) vs placebo in combination with caloric restriction and physician-managed behavior modification. Clin Pharmacol Ther 1986;39: 501–509
15. Altschuler S, Conte A, Sebok M, et al. Three controlled trials of weight loss with phenylpropanolamine. Int J Obesity 1982;6:549–556
16. Patient Management Protocol for the Use of Clozapine. Washington, DC: Dept Veterans Affairs, Veterans Health Administration; July 18, 1995. VHS&RA Circular 10-90-015
17. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
18. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
19. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
20. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
21. Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157:975–981
22. Goodall E, Oxtoby C, Richards R, et al. A clinical trial of the efficacy and acceptability of d-fenfluramine in the treatment of neuroleptic-induced obesity. Br J Psychiatry 1988;153:208–213
23. Soper HV, Elliott RO, Rejzer AA, et al. Effects of fenfluramine on neuropsychological and communicative functioning in treatment-refractory schizophrenic patients. J Clin Psychopharmacol 1990;10:168–175
24. Marshall BD, Glynn SM, Midha KK, et al. Adverse effects of fenfluramine in treatment refractory schizophrenia. J Clin Psychopharmacol 1989;9:110–115
25. Lake RC. Manic psychosis after coffee and phenylpropanolamine. Biol Psychiatry 1991;30:401–404
26. Marshall RD, Douglas CJ. Phenylpropanolamine-induced psychosis: potential predisposing factors. Gen Hosp Psychiatry 1994;16:358–360
27. Lake CR, Gallant S, Masson E, et al. Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. Am J Med 1990;89: 195–208
28. Boffi BV, Klerman GL. Manic psychosis associated with appetite suppressant medication, phenylpropanolamine. J Clin Psychopharmacol 1989;9: 308–309
29. Strauss A. Homicidal psychosis during the combined use of cocaine and an over-the-counter cold preparation [letter]. J Clin Psychiatry 1989;50:147

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