ELSEVIER

RESPONSE

Response: Negative Symptoms Redux

Carpenter et al. (2000) challenge the conclusion, in an article that mainly addresses the role of serotonin in antipsychotic drug action, that clozapine and other atypical antipsychotic drugs may improve primary negative symptoms in some patients with schizophrenia (Meltzer 1999). Neither that article, nor this response to their letter, provides an opportunity to fully address this important topic. We can only point out a few considerations to address the evidence they offer in support of their view and to support the conclusion noted above, which has been discussed in more detail elsewhere (Meltzer 1995).

As support for their belief that clozapine does not improve primary negative symptoms, Carpenter et al. (2000) cite the meta-analysis of Wahlbeck et al. (1999). However, that publication did not even attempt to differentiate primary vs. secondary negative symptoms. Furthermore, the only two conclusions of Wahlbeck et al (1999) concerning the effect of clozapine vs. typical neuroleptics on negative symptoms *in toto* were: (a) that only 4 of the 40 double-blind studies of clozapine vs. typical neuroleptics, involving a total of 164 participants, could provide useful data for comparing the effects of clozapine vs. other treatments on negative symptoms; and (b) that "the summary standard mean difference for effect on negative symptoms was 0.4 (95% confidence interval = 0.1–0.8) in favor of clozapine, but the small number of participants contributing to this result necessitates cautious interpretation of this statistically significant finding (emphasis added)." Thus, we fail to understand how this study supports the view of Carpenter et al. (2000). However, it is not clear, to us at least, why Wahlbeck et al. (1999) could find no more than four studies published between 1974 and 1988 which, they believe, satisfactorily address the effect of clozapine vs. a comparator on negative symptoms *in toto*, excluding, for example, the study by one of us and colleagues comparing clozapine with chlorpromazine (Kane et al. 1988), and many other double-blind studies which we believe are very informative about the effect of clozapine on negative symptoms, e.g., Claghorn et al. (1987). Furthermore, the statement by Carpenter et al. (2000) that the Wahlbeck et al. (1999) meta-analysis included the three studies which they claim were "specifically designed to test the effect of clozapine on negative symptoms as well as other such studies" is unlikely to be valid. Two of the three studies cited by Carpenter et al. (2000), i.e., Buchanan et al. (1998) and Rosenheck et al. (2000), in support of their argument that primary negative symptoms are not improved by clozapine, included 459 patients! The third, Conley et al. (1994) was an abstract reporting a study of 15 'deficit' and 35 'non-deficit' patients and was never published in full, to our knowledge. Carpenter et al. (2000) chose not to cite another meta-analysis of studies on the effect of the atypical antipsychotic drugs other than clozapine vs. typical antipsychotics (Leucht et al. 1999). Those authors concluded that both olanzapine and risperidone were superior to haloperidol and placebo with regard to the improvement of negative symptoms, whereas sertindole and quetiapine were superior to placebo only.

Although the distinction between primary and secondary negative symptoms is a valid one (see Kelley et al. 1999 for a particularly informative discussion), many others have pointed out (e.g., Tandon and Greden 1991; De Leon et al. 1992) that Carpenter et al. (2000) have never provided operational criteria to make the distinction. Yet, when others try to make this distinction, using methods such as path analysis or analysis of covariance which Carpenter et al. (1985) have sometimes themselves advocated, the validity of these approaches is challenged on no stronger grounds than the *theoretical* possibility that a source of 'unexplained variance' might have fatally confounded the interpretation of the data. How then to explain the sanguine attitude that Carpenter et al. (2000) have about the potential for treating negative symptoms represented by drugs thought to increase glutamatergic function. The effects noted with glycine and d-cycloserine in the cited papers (Goff et al. 1999b; Javitt et al. 1994) are very modest indeed compared to those frequently reported with the atypical antipsychotic drugs and have often not been replicated (Rosse et al. 1989; Potkin et al. 1999). Indeed, d-cycloserine has been

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reported to worsen negative symptoms in patients treated with clozapine (Goff et al. 1999a).

Many investigators have found that at least some types of primary negative symptoms do improve over time using a paradigm which Carpenter himself has acknowledged to one of us (HM) is more likely to detect improvement independent of changes in secondary negative symptoms, e.g., positive symptoms, extrapyramidal symptoms (EPS), and depression. This is a study design which includes only patients with moderate-severe negative symptoms, with few or no positive symptoms, depression, or EPS. We have reported on several occasion that clozapine is effective to reduce some but not all types of negative symptoms in these patients (Meltzer 1985, 1995, 1997).

There is a very large body of positive evidence using this model with amisulpride, a selective D2/D3 antagonist (Boyer et al. 1995; Pallière-Martinot et al. 1995; Rein and Turjanski 1997; Loo et al. 1997; Danion et al. 1999; Möller et al. 1995). Tollefson and Sanger (1997) have also provided similar data for risperidone and olanzapine, respectively, in addition to using path analysis, to adjust for the contribution of changes in secondary causes of negative symptoms in the major group of patients with schizophrenia, those with mixed symptomatology. A one year multicenter trial of ziprasidone (another atypical antipsychotic drug in the same pharmacological category as clozapine, risperidone, and olanzapine) vs. placebo in hospitalized patients with schizophrenia showed a clear effect of ziprasidone on negative symptoms that was independent of any change in positive symptoms, depression, or EPS (Arato et al. submitted). The dismissal of path analysis by Carpenter et al. (2000) contrasts with their praise of studies such as that of Rosenheck et al. (1999) which employ essentially the same type of analysis.

A second critical issue in studying the effect of antipsychotic drugs on negative symptoms is inclusion of subjects who have at least moderate levels of negative symptoms. We continue to find that there are significant decreases in ratings of SANS subscales: affective flattening, alogia, avolition, and anhedonia, due to clozapine, independent of changes in positive symptoms, depression, EPS, and cognitive improvement, in patients who meet deficit criteria, as well as those who do not (Meltzer 1985, 1991; Meltzer et al. in preparation). However, this improvement is noted only in those patients with higher initial severity of negative symptoms, similar to results with other pharmacologic agents which have been reported to improve negative symptoms, e.g., d-amphetamine (Sanfilipo et al. 1996). Space does not permit a full discussion of why this might be the case.

While we and others (Miller et al. 1994; The Collaborative Working Group on Clinical Trial Evaluations 1998) believe the evidence supports the conclusion that the atypical antipsychotic drugs are effective to some extent to treat primary negative symptoms, we think the evidence is strong that they are less able to improve negative than positive symptoms or cognition (Kane et al. 1988; Meltzer 1997; Galletly et al. 1999). Better treatments for negative symptoms are clearly needed and will, no doubt, be possible once more is understood about their pathophysiology. Thus, negative symptoms have been suggested to be due to decreased dopaminergic activity in the prefrontal cortex (Meltzer 1985; Davis et al. 1991) and to improve with amphetamine (van Kammen and Boronow 1988) which increases cortical dopamine release (Karoum et al. 1994); there is extensive evidence that clozapine and the other atypical antipsychotic drugs can enhance extracellular DA levels in the prefrontal cortex (Kuroki et al. 1998).

In conclusion, we believe that there is still considerable reason to conclude that clozapine and other atypical antipsychotic drugs are able to improve primary as well as secondary negative symptoms and that there is a plausible basis for this effect. However, we recognize that the mean effect is a weak one which requires appropriate subjects and well-trained raters to observe and distinguish from improvement in secondary negative symptoms.

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REFERENCES

Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F (1995): Treatment of negative symptoms in schizophrenia with amisulpride. Br J Psychiatry 166:68–72

Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter WT Jr (1998): Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. Am J Psychiatry 155:751–760

Carpenter WT Jr, Conley R, Kirkpatrick B (2000): On schizophrenia and new generation drugs. Neuropsychopharmacology, in press

Carpenter WT Jr, Heinrichs DW, Alphs LD (1985): Treatment of negative symptoms. Schizophr Bull 11:440–452

Claghorn J, Honigfeld G, Abuzzahab FS Sr, Wang R. Steinbook R, Tuason V, Klerman G (1987): The risks and benefits of clozapine versus chlorpromazine. J Clin Psychopharmacol 7:377–384

Conley R, Richardson C, Kent D, Gounaris C, Zaremba S (1994): Clozapine response varies in deficit vs. non-deficit schizophrenic subjects. Biol Psychiatry 35:746

Danion J-M, Rein W, Fleurot O, and The Amisulprid Study Group (1999): Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Am J Psychiatry 156:610–616

Davis KL, Kahn RS, Ko G, Davidson M (1991): Dopamine in schizophrenia: A review and reconceptualization. Am J Psychiatry 148:474–486

De Leon J, Simpson GM, Peralta V (1992): Positive and negative symptoms in schizophrenia: Where are the data? Biol Psychiatry 31:431–434

Galletly CA, Clark CR, McFarlane AC, Weber DL (1999): Effects of clozapine for non-treatment-resistant patients with schizophrenia. Psychiatric Serv 50(1):101–103

Goff DC, Henderson DC, Evins AE, Amico E (1999a): A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. Biol Psychiatry 45:512–514

Goff DC, Tsai G, Levitt J, Amico E, Manoach D, Schoenfeld DA, Hayden DL, McCarley R, Coyle JT (1999b): A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Archives of General Psychiatry 56(1):21–27

Javitt DC, Zylberman I, Zukin SR, Heresco-Levy U, Lindenmayer JP (1994): Amelioration of negative symptoms in schizophrenia by glycine. American Journal of Psychiatry. 151(8):1234–1236

Kane J, Honigfeld G, Singer J, Meltzer HY, and The Clozaril Collaborative Study Group (1988): Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796

Karoum F, Chrapusta SJ, Brinjak R, Hitri A, Wyatt RJ (1994): Regional effects of amphetamine, cocaine, nomifensine and GBR 12909 on the dynamics of dopamine release and metabolism in the rat brain. Br J Pharmacol 113:1391–1399

Kelley ME, van Kammen DP, Allen DN (1999): Empirical validation of primary negative symptoms: Independence from effects of medication and psychosis. Am J Psychiatry 156:406–411

Kuroki T, Meltzer HY, Ichikawa J (1998): Effects of antipsychotic drugs on extracellular dopamine levels in the medial prefrontal cotrex and nucleus accumbens. J Pharmacol Exp Therap 288:774–781

Leucht S, Pitschel-Walz G, Abraham D, Kissling W (1999): Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiaine, risperidone and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophrenia Res 35:51–63

Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O (1997): Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. Br J Psychiatry 170:18–22

Meltzer HY (1985): Dopamine and negative symptoms in schizophrenia: Critique of the Type I-Type II hypothesis. In Alpert M (ed), Controversies in Schizophrenia: Changes and Constancies. New York, NY, Guilford Press, pp 110–136

Meltzer HY (1991): Pharmacologic treatment of negative symptoms. In Greden JF, Tandon R (eds), Negative Schizophrenic Symptoms: Pathophysiology and Clinical Implications. Washington, DC, American Psychiatric Press, Inc, pp 214–231

Meltzer HY(1995): Clozapine: Is another view valid? Am J Psychiatry 152:821–825

Meltzer HY (1997): Treatment-resistant schizophrenia: The role of clozapine. Curr Med Res Opin 14:1–20

Meltzer HY (1999): The role of serotonin in antipsychotic drug action. Neuropsychopharmacology 21:106S–155S

Meltzer HY, Sommers AA, Luchins DJ (1986): The effect of neuroleptics and other psychotropic drugs on negative symptoms in schizophrenia. J Clin Psychopharmacol 6:329–338

Miller DD, Perry PJ, Cadoret RJ, Andreasen NC (1994): Clozapine's effect on negative symptoms in treatment-refractory schizophrenics. Comp Psychiatry 35:8–15

Möller HJ, Muller H, Borison RL, Schooler NR, Chouinard G (1995): A path-analytical approach to differentiate between direct and indirect drug effects on negative symptoms in schizophrenic patients. A re-evaluation of the North American risperidone study. Eur Arch Psych Clin Neurosci 245:45–49

Pallière-Martinot ML, Lecrubier Y, Martinot JL, Aubin F (1995): Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. Am J Psychiatry 152:130–134

Potkin SG, Jin Y, Bunney BG, Costa J, Gulasekaram B (1999): Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. Am J Psychiatry 156:145–147

Rein W, Turjanski S (1997): Clinical update on amisulpride in deficit schizophrenia. Intl Clin Psychopharmacol 12(Suppl 2):S19–S27

Rosenheck R, Dunn L, Peszke M, Cramer J, Xu W, Thomas J, Charney D (1999): Impact of clozapine on negative symptoms and on the deficit syndrome in refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. Am J Psychiatry 156(1):88–93

Rosse RB, Theut SK, Banay-Schwartz M, Leighton M, Scarcella E, Cohen CG, Deutsch SI (1989): Glycine adjuvant therapy to conventional neuroleptic treatment in schizophrenia: An open-label, pilot study. Clin Neuropharmacol 12:416–424

Sanfilipo M, Wolkin A, Angrist B, van Kammen DP, Duncan E, Wieland S, Cooper TB, Peselow ED, Rotrosen J (1996): Amphetamine and negative symptoms of schizophrenia. Psychopharmacology 123:211–214

Tandon R, Greden J (1991): Negative symptoms of schizophrenia: The need for conceptual clarity. Biol Psychiatry 20:321–325

The Collaborative Working Group on Clinical Trial Evaluations (1998): Assessing the effects of atypical antipsychotics on negative symptoms. J Clin Psychiatry 59:23–27

Tollefson GD, Sanger TM (1997): Negative symptoms: A path analytic approach to a double-blind, placebo-and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 154:466–474

van Kammen DP, Boronow JJ (1988): Dextro-amphetamine diminishes negative symptoms in schizophrenia. Intl Clin Psychopharmacol 3:111–121

Wahlbeck K, Cheine M, Essali A, Adams C (1999): Evidence of clozapine's effectiveness in schizophrenia: A systematic review and meta-analysis of randomized trials. Am J Psychiatry 156:990–999