
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

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 occasions 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 (Sanfilippo 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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