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LETTER TO THE EDITOR

On Schizophrenia and New Generation Drugs

Meltzer presents an informative review of antipsychotic drug action and serotonin (Meltzer 1999). However, his conclusion that new generation drugs with serotonin antagonism are efficacious for the primary negative symptoms of schizophrenia contrasts with our view (Carpenter 1995; Carpenter et al. 1995) and merits further consideration.

It is important to distinguish primary, or disease-based, negative symptoms from negative symptoms secondary to other sources (e.g., depressive anhedonia, neuroleptic akinesia, paranoid social withdrawal, sedative anergia) (Carpenter et al. 1998, 1993). The clinical trials cited by Meltzer (1999) do not make this distinction. Other studies have addressed primary negative symptoms by design and fail to support the efficacy hypothesis for clozapine (Buchanan et al. 1998; Conley et al. 1994; Rosenheck et al. 1999). A meta-analysis of these and other studies reaches similar conclusions (Wahlbeck et al. 1999). The view that new generation medications are not a therapeutic answer for trait negative symptoms of schizophrenia is further reinforced in the six-month controlled study in outpatients where neither haloperidol nor clozapine was associated with negative symptom improvement (Schooler et al. 1999), and in studies by Lieberman et al. (1994) and Tandon et al. (1993) where improvement appeared to be accounted for by secondary negative symptoms. Conley et al. (1998) also failed to observe negative symptom improvement with olanzapine. It is important to note that superior efficacy for psychosis was shown in each of the clozapine studies, so the lack of efficacy for negative symptoms was not a non-responsive cohort effect.

Meltzer suggests a direct effect on primary negative symptoms with risperidone and olanzapine, but this is based on path analysis where some, but not all, sources of variance are in the model (Moller et al. 1995; Tollefson and Sanger 1997). The hypothesized direct effect in these studies is based upon the statistical term "unexplained variance." There are two problems with the assumption that unexplained variance is due to a direct therapeutic effect: 1) a reasonably thorough list of the causes of secondary negative symptoms has not been included in these equations; and 2) there are many sources of "noise" in a clinical trial which contribute to unexplained variance.

The distinction between primary and secondary negative symptoms has theoretical and practical importance (Carpenter et al. 1993, 1999). We believe that as yet there is no proven treatment for the avolitional pathology described by Kraepelin (1971), and serotonin antagonism is not a promising lead. More interesting are results from study designs which isolate trait or deficit negative symptoms, and suggest a role for glutamatergic mechanisms in achieving a negative symptom response independent of an antipsychotic response (Goff et al. 1995, 1999; Heresco-Levy et al. 1996, 1999; Javitt et al. 1994). Observations in a d-serine trial also appear supportive, but negative symptom improvement coincided with improvement in psychosis, and the primary/secondary issue is not resolved (Tsai et al. 1998).

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