

Pharmacological Management of Prodromal and First Episode Schizophrenia

The optimal time to treat schizophrenia is as early in the course and as close to the onset as possible. Often the onset of the illness precedes by considerable periods of time the manifestation of symptoms that are diagnosable at the syndromal level. The onset of the formal symptoms of schizophrenia is generally preceded by a prodromal phase. So-called prodromal symptoms and behaviors (i.e. those that herald the approaching onset of the illness) include attenuated positive symptoms (e.g., illusions, ideas of reference, magical thinking, superstitiousness), mood symptoms (e.g., anxiety, dysphoria, irritability), cognitive symptoms (e.g., distractibility, concentration difficulties), social withdrawal or obsessive behaviors to name a few.(McGlashan, 1996; Yung and McGorry, 1996). Because many of these prodromal phenomena extensively overlap with the range of mental experiences and behaviors of persons in the ages of risk who do not subsequently develop schizophrenia, prodromal symptoms cannot be considered diagnostic. It is precisely their non-specificity and lack of high predictive validity that limits their utility for the purposes of early intervention.

The development of frank psychotic symptoms marks the formal onset of first-episode schizophrenia, although this is usually not diagnosed for some time until the patient seeks or is brought to medical attention. Indeed, the duration of psychotic symptoms prior to diagnosis and treatment averages about one year and if time since prodromal symptoms first appeared are considered the average duration is about three years.(McGlashan, 1996). Despite this most individuals recover symptomatically from the first episode.

Acute Treatment

Treatment Selection and Dosing of Pharmacologic Agents for Early Stages of Schizophrenia

The pharmacology of treating the prodromal stages of schizophrenia and related psychotic disorders has not been sufficiently well developed. In the absence of adequate evidence the recommended approach is symptomatic treatment of prodromal symptoms with the appropriate agent(s) including anxiolytic, antidepressant and antipsychotic drugs. If an antipsychotic drug is to be used, the general consensus is that this be one of the atypical antipsychotic drugs (Chakos et al, 1992; Lieberman et al, 2003b) Currently, there are no specific guidelines or sufficient evidence to determine which of these drugs to use. Side effects are the primary distinguishing features among the various drugs.

Young patients without prior exposure to antipsychotic drugs may be more sensitive to the antipsychotic side effects than patients in other stages of the illness (Lehman and Steinwachs, 1998). Lower doses of antipsychotics, e.g 1- 2 mg/day of risperidone, 40-80 mg/day of ziprasidone or 5-10 mg/day of olanzapine, may be adequate to achieve positive symptom remission, but less likely to cause side effects. (Chakos et al., 1992; Merlo et al., 2002). Younger patients are more susceptible to the side effects of antipsychotic drugs ranging from extrapyramidal symptoms and hyperprolactinemia to weight gain and metabolic effects (Kopala et al., 1996). The Schizophrenia Patient Outcomes Research Team (Lehman and Steinwachs, 1998) recommended that patients in a first psychotic episode should be treated with relatively lower doses (300-500 mg chlorpromazine equivalents per day) of antipsychotics than for patients with schizophrenia in general (300-1,000 mg chlorpromazine equivalents per day).

Since the first episode is a time when patients form their attitudes about treatment, efforts to minimize unpleasant side effects may influence patient's willingness to take medications long term. In a study of first episode patients, the only variable that predicted whether patients would attend a follow up assessment was antipsychotic dose, with those on higher doses less likely to comply (Jackson et al. 2001).

While positive symptoms in first episode patients tend to respond well to antipsychotic drug treatment, negative and cognitive symptoms of schizophrenia generally take longer to respond or are less responsive to antipsychotic medications (Kopala et al., 1996; Sanger et al, 1999; Group, 1987) Negative and cognitive symptoms may have a different time course for response than positive symptoms. In addition, the relative refractoriness of negative and cognitive symptoms may contribute to the less than optimal functional recovery that is often observed in first episode patients.

Adjunctive Treatments of Residual Symptoms and Comorbid Syndromes

Often antipsychotic medications are insufficient by themselves to achieve full symptom remission and functional recovery in early stage schizophrenia patients. For these reasons, a variety of adjunctive treatments both pharmacologic and non-pharmacologic can be used to enhance and optimize treatment response. Adjunctive treatments have different roles in the management of first episode schizophrenia-targeting residual symptoms and treating co-morbid syndromes.

Depressive syndromes are common in prodromal and first episode patients. Patients who ultimately manifest symptoms of schizophrenia often report a previous depressive episode⁵⁹ and/or suicide attempt in their prodromal period (Cohen et al., 1994). Depressive symptoms will often resolve as psychotic symptoms remit (Koenen et al., 1993). However, in some cases they may persist or occur in the episode's aftermath ("post-psychotic depression"). Antidepressants should be used cautiously in prodromal and first episode schizophrenia as they could possibly provoke or exacerbate psychotic symptoms. Though its use in first episode schizophrenia has been studied recently (Lieberman et al., 2003a), clozapine is not considered at this time a first line drug for first episode schizophrenia. It should be considered early in the course of treatment only in patients who are unresponsive to other second generation antipsychotic drugs.

2. Treatment after remission of prodromal and first episode schizophrenia

Continuation and maintenance treatment

The need for interventions aimed at achieving functional recovery is reflected by the poor outcomes found in studies of first episode patients (Robinson et al., 1999; 2000; Harrison et al., 2001). While patients typically recover from a first episode of schizophrenia, the long-term course for most patients is still characterized by chronic illness, disability, and relapse.

After achieving maximal therapeutic response, how long should treatment (particularly pharmacologic treatment) be continued? There are not sufficient data to answer that question in prodromal patients. Thus, treatment of prodromal symptoms should be considered as time limited and aimed to alleviate current symptoms and stabilize the patient. On the other hand there is a growing body of evidence in first episode patients that suggests the value of continuing medication for a sustained and possibly indefinite period in first episode patients.

The risk of eventual relapse after recovery from a first psychotic episode is very high and is greatly diminished by maintenance antipsychotic treatment. (Kane et al., 1982; McCreadie et al., 1989). However, even with strong evidence of the risk of relapse without antipsychotic medication, there is still no clear consensus on the recommended duration of treatment for patients who have recovered from a first episode of schizophrenia. Clinicians may have a difficult time convincing patients who have recovered from one episode of schizophrenia that indefinite and possibly life-long antipsychotic treatment is indicated because of the diagnostic uncertainty and instability associated with a first psychotic episode, limited patient

understanding and awareness of the illness, and risks of long term antipsychotic therapy. Treatment of patients who have remitted from a first episode of schizophrenia is generally recommended for at least one year. If at the end of that time patients have been symptom-free they can be considered for a trial period without medication, provided that dose reductions are made gradually over several months with frequent visits of the small minority who maintain remission without pharmacotherapy have not yet been identified.

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