Maintenance therapy in schizophrenia: a critical comment

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Abstract

The paper's aim was to evaluate a rationale for maintenance therapy in schizophrenia and to consider the feasibility of intermittent targeted therapy as an alternative treatment strategy. This was achieved by a selected review of the relevant English-language literature published since 1966 through a Medline search and cross-referencing. Current scientific evidence for continuous maintenance therapy in schizophrenia was found equivocal as the randomization in clinical trials lumped together heterogeneous groups of patients, thereby creating a wide gap between research and clinical practice. In addition, the majority of studies took a narrow view of the concept of relapse. For these reasons, targeted intermittent treatment was probably prematurely discarded altogether. The rationale for use and optimal duration of maintenance antipsychotic pharmacotherapy for schizophrenia has not been adequately validated. The construct validity of outcome indicators currently used in maintenance treatment studies in schizophrenia should be reconsidered. Intermittent targeted treatment may represent a viable option in some clinical situations and warrant further evaluation. With the widespread use of atypical antipsychotics, current long-term maintenance strategies may need a reappraisal.

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Introduction

Schizophrenia remains one of the major challenges for psychiatry in the 21st century. While new antipsychotic drugs have widened the scope of therapeutic options and neuropsychiatric research has increased our understanding of the neurobiology of schizophrenia, there is still no clear answer to the question frequently asked by patients, 'When can I come off the medication?' Existing guidelines vary with respect to the recommended duration of prophylactic treatment for schizophrenia. For instance, the Dutch consensus statement recommends 2-yr prophylaxis for first-episode cases and 5-yr prophylaxis for two or more episodes (McGlashan, 1998). The American Psychiatric Association recommends prophylactic treatment for about 1 yr after a first episode, while patients with two or more episodes should be on maintenance medication for at least 5 yr (APA, 1997). All these recommendations are somewhat arbitrary based on medium-term follow-up studies lasting less than 3 yr. A recent review argued that 5-yr maintenance is not adequate in view of the life-long vulnerability to relapse, risk of chronicity and the serious consequences of relapse for patients' lives. Long-term maintenance was thus recommended although the duration cannot be scientifically defined (Bosveld-van Haandel et al., 2001). In this paper, we shall reconsider the arguments for and against the use of maintenance therapy with special reference to its main alternative, targeted intermittent treatment.

Validity of current evidence for maintenance treatment

Early, randomized placebo-controlled trials with 1–2 yr follow-up demonstrated lower relapse rates in patients on maintenance antipsychotic treatment than those withdrawn from medication (Crow et al., 1986; Kane et al., 1982). In a meta-analysis of placebo-controlled studies of neuroleptic withdrawal after acute treatment (Gilbert et al., 1995), 66 studies between 1958 and 1993 were reviewed involving 4365 patients, of whom 3141 were 'withdrawn' and 1224 continued with maintenance medication. All studies after 1981 employed standardized diagnostic criteria. Thirty-seven studies were double-blind controlled trials using placebo for 'discontinuation' in 12 studies, while the rest involved control groups of patients who continued treatment. The tapering period lasted 2-60 d with a follow-up period of 0.5–24 months.
The relative rate of relapse was three times higher in the discontinuation group. This is the most robust scientific evidence to date supporting maintenance therapy for up to 2 yr. More recent studies (Gaebel et al., 2002; Gitlin et al., 2001; Robinson et al., 1999; Viguera et al., 1997; Wiedemann et al., 2001) have generally confirmed these earlier findings reviewed by Gilbert et al. (1995). Among these recent studies, the relapse rates of first-episode schizophrenia (Gitlin et al., 2001; Robinson et al., 1999) in discontinuation groups were significantly higher, consistent with results using multiple-episode cases.

The above findings seemed to suggest that maintenance therapy was the evidence-based superior option of treatment for first-episode and multiple-episode schizophrenic patients. However, the opposite view of the data from Gilbert et al.’s (1995) meta-analysis has often been neglected. The authors reported that the relapse rate actually ranged from 0 to 100%; in fact, 50% of patients in the discontinuation group did not relapse, while 15.6% of the maintenance group relapsed within 1 yr. Also, the difference in relapse rates between the two groups decreased over time. The neuropsychological profile of the two groups in terms of the Wechsler Adult Intelligence Scale IQ and trail-making test showed minimal differences except for the domain of attention and concentration, with the maintenance group tending to do better. The average treatment response after reinstitution of antipsychotic medication ranged from 3 d to 3 wk. There was no specific predictor of outcome identified, except length of follow-up. With few recent exceptions (e.g. Gaebel et al., 2002; Gerlach and Larsen, 1999; Wiedemann et al., 2001), patients’ subjective experiences and their quality of life, plus numerous other factors, have not been evaluated in these studies.

An important confounding factor, i.e. the mode of neuroleptic withdrawal, is often not emphasized in discontinuation studies. A substantial proportion of studies employed abrupt discontinuation of oral antipsychotic medication which increased relapse rate compared to gradual withdrawal, particularly in the first 6 months following discontinuation (Viguera et al., 1997). This fact is all the more important as the risk of relapse receded for most patients after 6 months (Viguera et al., 1997).

Several conclusions can be drawn from the above data. First, wide variations in relapse rate following discontinuation of antipsychotic treatment suggest that the study populations were very heterogeneous, and the significantly elevated relative risk for relapse in the discontinuation group was based on data with a wide confidence interval, i.e. weak scientific validity. Secondly, the fact that the only specific predictor of outcome was the length of follow-up suggests that maintenance therapy had not robustly altered the medium-term outcome of schizophrenia. Thirdly, equivocal results obtained from comparing the two groups with respect to neuropsychological profile reminds us that there are important outcome criteria in addition to the rather loosely defined ‘relapse’. In fact, Gilbert et al. (1995) pointed out that ‘relapse’ was not properly defined in 22 studies, while in 11 studies ‘relapse’ simply meant ‘return to active treatment after discontinuation’. The remaining 33 studies defined ‘relapse’ as behavioural worsening and change in scores on the Brief Psychiatric Rating Scale. Finally, the reported prompt recovery rate following reinstitution of treatment after treatment withdrawal indicates that intermittent targeted therapy may be a feasible option in the long-term pharmacological treatment of schizophrenia, at least in a proportion of cases. Some recent evidence showed that close clinical monitoring and a low threshold for reinstating medication could prevent hospitalization for the majority of cases (Gitlin et al., 2001).

Course of schizophrenia in the era of antipsychotic treatment

Advocates of maintenance therapy concede that recommendations are based primarily on investigations with a follow-up period of 2–3 yr or less. The paucity of longer-term studies makes it difficult to predict what constitutes the optimal duration of treatment. As pointed out earlier, the difference in relapse rate between discontinuation and maintenance therapy tended to diminish over 2 yr, and the only outcome predictor was length of follow-up rather than treatment modality. The long-term prognosis for schizophrenia seems to be affected by multiple factors too complex to be determined individually. Ram et al. (1992) reviewed 34 studies on the outcome of first-admission schizophrenia spanning both the pre-treatment and modern treatment eras. Based on these studies that were heterogeneous with respect to methodology, the evidence for alteration in course of illness by antipsychotic treatment was inconclusive and outcome predictors were variable. Overall outcome was rather gloomy, with a relapse rate of 60%. Similarly, taking into account historical changes in diagnostic criteria, Hegarty et al. (1994) reported stable clinical improvement rates for schizophrenia patients through the pre- and post-treatment era in their meta-analysis of 821 studies published from 1895 to 1992.

There is some preliminary evidence that continuous maintenance treatment may not have a major impact on the long-term outcome of schizophrenia (Bleuler, 1978; Ciompi, 1980). In a recent study, cessation of maintenance treatment in a subset of good-prognosis patients did not
alter the course of illness over a 4-yr period (Lerner et al., 1995). Others described chronic patients who sustained remission over 15 yr without antipsychotic medication (Fenton and McGlashan, 1987). The question that should be posed, therefore, is whether continuous maintenance antipsychotic treatment is justified for every patient with schizophrenia.

Evidence on intermittent targeted treatment

There have been few studies on the efficacy of targeted intermittent treatment and study samples are small. Herz et al. (1991) evaluated targeted treatment as an alternative to maintenance therapy in a group of stable schizophrenic outpatients who had completed an 8-wk washout period. The overall findings based on non-blind observation of 13 stabilized patients over 13–45 wk demonstrated the feasibility of a targeted treatment approach. In a 2-yr prospective, single-blind, randomized controlled trial involving 116 outpatients with chronic schizophrenia, Carpenter et al. (1990) demonstrated that 36% of the ‘continuous’ group relapsed compared to 53% of the ‘targeted’ group. Patients in the targeted group used significantly lower doses of drugs. Other measures of psychopathology or functioning at 1 and 2 yr failed to differentiate the two groups. Similarly, further studies each involving more than 300 patients (Gaebel, 1994; Schooler et al., 1997) showed that the relapse rate in the targeted group was higher than in the continuous group, i.e. 30–40% in the former vs. 25–30% in the latter. These investigators also concluded that side-effect profiles and social functioning were similar in the two groups.

There is preliminary evidence that first-episode patients fare equally well with continuous and targeted maintenance therapy in a 2-yr period in terms of psychopathology, social adjustment, subjective well being and side-effects, while prodrome-based targeted treatment seemed to have an advantage concerning cumulative doses and treatment adherence (Gaebel et al., 2002).

Although the improvement in clinical outcome in the continuous group was statistically significant, the difference was only marginal and of questionable clinical significance. The discontinuation groups did not differ in other outcome parameters including daily functioning. Controlled trials cited above failed to address a host of prognostic factors including patients’ subjective experiences and acceptance of medication (Gerlach and Larsen, 1999; Van Putten et al., 1981), mode of withdrawal of antipsychotic drugs (Vigueria et al., 1987), global functioning (Gaebel et al., 2002) and quality of life, as well as severity of psychopathology, course and length of illness (Crow et al., 1986; Lerner et al., 1995), affective symptoms (Fenton and McGlashan, 1987), alcohol and drug abuse (Ayuso-Gutierrez et al., 1997), side-effect profile (Liebermann et al., 1994), premorbid social adjustment (Fenton and McGlashan, 1987) expressed emotions (Wiedemann et al., 2001), stressful life events (Hirsch et al., 1996) and the role of therapeutic alliance (Frank and Gunderson, 1990). These are important confounding variables for clinical outcome measures such as ‘relapse’.

Promising earlier efforts to identify relapse-prone patients with biological tests (Liebermann et al., 1994; van Kammen et al., 1996) have not been followed up and utilized in predicting relapse and planning long-term pharmacotherapy.

There is a fundamental flaw in all the randomized controlled studies examining the effects of discontinuation or comparing continuous with intermittent maintenance treatment; namely, that they failed to take into account the clinical heterogeneity of schizophrenia. Although not a randomized trial, the only exception has been the study of Lerner et al. (1995) that examined the influence of changes in treatment on the patterns of relapses in a 4-yr open-label, prospective controlled trial. A total of 220 outpatients with remitting schizophrenia were given individualized treatment based on the previous course of illness, and current psychopathology. Schizophrenia patients presenting with chronic course and permanent residual symptomatology requiring continuous maintenance medication were excluded from the study. Individualized treatment significantly decreased the frequency of relapses in patients with frequent relapses whilst complete cessation of antipsychotic treatment did not lead to increased frequency of relapses in patients with rare relapses who were also symptom-free between relapses. The results of Lerner et al. (1995) suggest that optimal clinical decisions as well as randomization in clinical trials cannot be made without consideration of multiple factors, including characteristics of the psychopathology and course and length of illness.

‘Relapse’ has typically been used as chief outcome indicator in the above-mentioned studies. However, the construct validity of ‘relapse’ has seldom, if ever, been questioned. In other words, the impacts of ‘clinical relapse’ on patients’ lives from their own perspectives are uncertain. For instance, relapse often has different meanings in socio-cultural contexts as evidenced by the International Pilot Study of Schizophrenia (Leff et al., 1992; WHO, 1973) that revealed marked discrepancies in social and clinical outcome between developed and developing countries over 5 yr.

An ethical dilemma arises in considering whether patient-perceived outcome or clinician-perceived outcome should be emphasized. Patients often choose their preferred course of treatment by defaulting on prescribed
maintenance therapy. Outside the domain of compulsory treatment orders, patients should be able to make their own choices, even those that appear unreasonable. Refusing to accept patients’ decisions would also undermine therapeutic alliance. For cases where discontinuation and intermittent treatment are inevitable due to patients’ choices, clinicians need scientific data about the feasibility and acceptability of treatment discontinuation with respect to clinical outcomes.

In conclusion, the gap between research and clinical reality necessitates consideration of multiple prognostic factors when deciding for or against long-term maintenance treatment in any given patient, rather than relying solely on results of randomized controlled trials that compared heterogeneous groups of patients selected only on the basis of diagnosis. To this end, ‘relapse’ in a strict, clinical–symptomatic sense ought not to be used as the only outcome indicator in determining the optimal long-term treatment modality. Hence, quality of life, socio-occupational functioning, side-effect profiles and health-related costs should be brought into the risk–benefit consideration as well as in the concept of relapse. Future research should also more broadly define clinical dimension of ‘relapse’ using reliable standardized assessment tools. ‘Relapse’ should be understood as having different degree of severity starting from (1) minor, non-specific symptomatic changes not amounting to the re-emergence or worsening of psychotic symptoms, to (2) return or worsening of psychotic symptoms (symptomatic relapse or exacerbation) and (3) major symptomatic changes leading to serious clinical consequences in terms of re-hospitalization and/or closely supervised active treatment (full clinical relapse). Intermittent targeted treatment should not be prematurely discarded and can be justified if other options are not feasible. This may particularly hold true in selected cases, such as those having few past relapses, good inter-episode functioning, history of prompt recovery after restitution of antipsychotic treatment and good therapeutic alliance with the therapist. At present such a recommendation is still not substantially evidence-based. More good prognostic factors will have to be ascertained in future case-controlled trials on the efficacy and safety of intermittent targeted therapy in order to accurately identify a subset of patients who may benefit from this treatment modality.

All the studies mentioned in this paper originate before the introduction of novel antipsychotic drugs. With the widespread use of atypical antipsychotics, current long-term maintenance strategies may need revision; whether the long-term use of atypical drugs will promote continuous or targeted maintenance treatment or will lead to new strategies remains to be seen. However, compelling evidence on medical complications (Dixon et al., 2000; Kinon et al., 2001) associated with long-term use of atypical antipsychotics such as weight gain and diabetes mellitus warrants consideration as important outcome parameters in studies on maintenance therapy with atypical antipsychotic drugs.

References


