Long-Term Adaptive Life Functioning in Relation to Initiation of Treatment with Antipsychotics over the Lifetime Trajectory of Schizophrenia

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Background: There is evidence that the stage of illness at which antipsychotic treatment is initiated in schizophrenia may have consequences for its subsequent course. How this might relate to impaired adaptive life functioning in the long-term is poorly understood.

Methods: Thirty-eight inpatients, many of whom had been admitted in the preneuroleptic era, were assessed using the Social-Adaptive Functioning Evaluation (SAFE); constituent clinical and medication phases of the lifetime trajectory of their illnesses were then analyzed to identify predictors of SAFE score using multiple regression modeling.

Results: The primary, independent predictor of SAFE score was duration of initially unmedicated psychosis, which accounted for 22% of variance (p < .001) therein. Conversely, duration of subsequently treated illness, although decades longer, failed to predict SAFE score.

Conclusions: These findings are consistent with some form of “progressive” process, particularly over the first several years following the emergence of psychosis, which is associated with accrual of deficits in adaptive life functioning. Biol Psychiatry 2000;48:163–166 © 2000 Society of Biological Psychiatry

Key Words: Schizophrenia, adaptive life functioning, initially unmedicated psychosis, long-term outcome

Introduction

That outcome in schizophrenia might be influenced by the stage of illness at which treatment with antipsychotics was initiated is attracting renewed attention. One proposition (Birchwood et al 1997; McGlashan and Johannessen 1996; Wyatt 1991) is that delayed intervention with antipsychotics may be associated with poorer outcome. For example, in first-episode studies, increasing duration of untreated psychosis appears to be associated with a longer time to remission, poorer quality of remission, and increasing likelihood of subsequent relapse (Loebel et al 1992; Szymbanski et al 1996). Our alternative approach has been to study a naturalistic circumstance that has resulted in patients who have experienced prolonged periods of initially unmedicated psychosis and in whom correlates thereof might be most prominent. Specifically, we have studied older patients who became ill in the preneuroleptic era and therefore endured many years of illness before antipsychotics were introduced.

In an initial study of this type, increasing duration of initially unmedicated psychosis appeared to be associated with increasing severity both of negative (but not positive) symptoms and of general (but not executive) cognitive impairment (Scully et al 1997b). Nonetheless, the nature of such associations within the overall lifetime trajectory of schizophrenia (Waddington et al 1998, 1999) and, in particular, any impact in terms of long-term outcome at a functional level, are poorly understood. In our study, we evaluated such patients for adaptive life functioning and, as an anchor to our previous study, for general and executive cognitive function. In addition, we resolved the patients’ lifetime illness trajectory in a novel manner into its sequential phases: from birth to onset of psychosis, through initiation of antipsychotics, to subsequently medicated illness in terms of both the duration of antipsychotic treatment and of interpolated drug-free intervals, and to index assessments at their current age. Some exploratory studies of craniofacial dysmorphogenesis, a putative index of early neurodevelopmental adversity (Lane et al 1997; Waddington et al 1999) and of neurological soft signs as an additional index of such compromised brain function (Lane et al 1996; Waddington et al 1998) also were made. Thereafter, we have applied multiple regression modeling to identify which phase(s) of illness might independently predict functional outcome measures; a particular hypothesis to be tested was that increasingly delayed intervention with antipsychotics would be a primary predictor of poorer adaptive life functioning in the long term.
Methods and Materials

This study involved 41 inpatients in St. Davnet’s Hospital, Monaghan, a long-term care facility in rural Ireland, who satisfied the Washington University criteria of Feighner and colleagues (1972) for schizophrenia. These individuals were the survivors (85%) among the 48 patients studied previously by Scully et al (1997b); the remaining cases were deceased through natural causes. Patient records were reviewed to determine demographic and medication variables. Age at onset was operationalized as age at first recorded contact with a psychiatric service, and duration of initially unmedicated psychosis as the time from age at onset to age at first recorded prescription of an antipsychotic; thereafter, duration of antipsychotic treatment and of interpolated antipsychotic-free intervals were determined from the same records. Adaptive life functioning was assessed using the Social-Adaptive Functioning Evaluation (SAFE). This 17-item instrument defines in increasing scores the severity of impairment in critical adaptive functioning domains, such as self-care, interpersonal competence and adjustment, and miscellaneous life skills such as cooperativeness. The SAFE is designed specifically for geriatric patients with chronic psychiatric illness in an institutional setting; ratings are made through observation, caregiver interviews, and patient interactions (Harvey et al 1997). General cognitive function was assessed using the Mini-Mental State Examination (MMSE; Folstein et al 1975); executive (frontal; Smith and Jonides 1999) cognitive function was assessed using the Executive Interview (EXIT; Royall et al 1992), which is designed specifically for patients such as those studied here whose debilities preclude the use of instruments such as the Wisconsin Card Sorting Test (Royall et al 1992, 1993; Scully et al 1997a, 1997b). Additionally, in preliminary studies, we also explored the feasibility of assessing such patients for neurological soft signs (NSS) using the Neurological Evaluation Scale (Buchanan and Heinrichs 1989) and the Condensed Neurological Examination (Rossi et al 1990) and for craniofacial dysmorphogenesis using an anthropometric scale (Lane et al 1997).

In the primary, hypothesis-based analysis, SAFE score was set as the outcome variable, and multiple regression modeling was applied to identify independent predictor variables among the indicated temporal phases of illness and treatment, current medication, and demographic indices.

Results

Complete data on each of the primary study variables were available for 38 of the 41 patients (93%) and it is to this group that all further discussion relates. Patients were generally older and characterized by poor social-adaptive functioning, with general and executive cognitive impairment (Table 1).

As indicated in Table 2, increasing SAFE score (greater functional impairment) was predicted prominently \( p < .001 \) by increasing duration of initially unmedicated psychosis, which accounted for 22% of variance; by older age at onset \( p = .003 \), which accounted for 3% of variance; and by lower current dose of antipsychotics \( p = .01 \), which accounted for 6% of variance. No other variable made any significant independent contribution to the regression model, which accounted for 68% of variance in SAFE score. Decreasing MMSE score (greater general cognitive impairment) was predicted only by increasing duration of initially unmedicated psychosis \( \beta = -0.55, SE\beta = 0.13, SE\beta = 4.12, p < .001, R^2 = 31\% \); no other variable made any significant independent contribution to a regression model, which accounted for 47% of variance in MMSE score. No variable made any significant independent contribution to a regression model for EXIT score, which accounted only for 14% of the variance. In exploratory analyses, increasing NSS score (greater neurological abnormality) was predicted only by duration of initially unmedicated psychosis \( p < .02 \); however, NSS were difficult to evaluate in these highly impaired patients because of problems in following examination instructions (only \( n = 28 \) were able to comply), hence scores may reflect these deficits. Using prominence of palatal abnormalities and reduced mouth width as initial indices of craniofacial dysmorphogenesis in schizophrenia (Lane et al 1997), which were also difficult to evaluate in these patients (only \( n = 35 \) able to comply), neither variable showed any material association with outcome measures.

Discussion

One of the main determinants of poor long-term outcome in schizophrenia is impairment in adaptive life functioning, whereby many patients exhibit inability to care for themselves and thus become dependent on others. The causes of these deficits are multifactorial and involve negative symptoms, positive symptoms, cognitive dysfunction, and the interactions between them, together with additional clinical, psychological, social, and situational
factors (Harvey et al 1997). In our study, we have examined the lifetime trajectory of older inpatients with chronic schizophrenia by disassembling current age into sequential, temporal phases of illness. Among these constituent temporal phases and other study variables considered, duration of initially unmedicated psychosis was a primary, substantive, and independent predictor of impairment in adaptive life functioning. This impairment also was associated with lower current dosage of antipsychotics, which may reflect less recourse to aggressive antipsychotic therapy with increasing disability, and with older age at onset. As an “anchor” finding, in confirmation of our previous report (Scully et al 1997b), duration of initially unmedicated psychosis was the primary predictor of general (but not of executive) cognitive dysfunction. Our study extends adverse correlates of delayed intervention with antipsychotics from the psychological into the day-to-day functional domain that is responsible for placing great personal and economic demand on health and social services.

It should be considered whether early impairment in adaptive life functioning might be associated, at least in part, with some delay in initiating antipsychotic therapy, although this issue is far from straightforward. Antipsychotics became available in rural Ireland only in the late 1950s, with the majority of the present patients receiving such medication for the first time into the 1960s. At admission, patients were acutely psychotic without evidence of the severity of their current impairments in adaptive life functioning. It may be more informative that duration of subsequently treated illness, although decades longer, failed to predict impairment in adaptive life functioning. The essential abandonment of insulin coma, reserpine, and electroconvulsive therapies, which some of these patients received over the preneuroleptic era but which proved difficult to quantify, suggests that any contribution from such “treatments” would be small relative to that of antipsychotic drugs. Any separate contribution from medical comorbidity remains to be isolated.

Taken together, the present data elaborate the notion (Birchwood et al 1997; Loebel et al 1992; McGlashan and Johannessen 1996) of the early phase of psychotic illness as a vulnerable period over which adverse biologic and psychosocial changes occur; thus, psychosis over this phase may reflect, at least in part, a process that is associated with increasing impairment unless ameliorated by antipsychotics. Factors operating over later phases of illness are also likely to influence long-term outcome, however. The present findings are consistent with some form of “progressive” process (Waddington et al 1998), particularly over the first several years following the emergence of psychosis, which is associated with accrual of functional deficits that encompass self-care, interpersonal competence and adjustment, and life skills, but which may be mitigated in part by early and effective intervention with antipsychotics. Nonetheless, the extent of variance in SAFE score that is accounted for by duration of initially unmedicated psychosis would indicate that functional outcome is influenced also by additional factors, which may be remediable by medication or alternative interventions. The present inpatient population has the advantage of considerable homogeneity for overall course of illness; however, the extent to which findings deriving from inpatients of this age and chronicity might generalize to other patient groups (including those remitting spontaneously or discharged from hospital and treated in the community) and the nature of any “progressive” process remain to be determined.

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**References**


