Schizophrenia Bulletin vol. 31 no. 3 pp. 650–671, 2005
doi:10.1093/schbul/sbi031
Advance Access publication on July 8, 2005

First-Episode Psychosis: Psychopathology, Quality of Life, and Functional Outcome

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The burgeoning interest in investigating the first episode of schizophrenia and related disorders provides an opportunity to examine how this approach has assisted our understanding of the heterogeneity of psychopathology of this disorder and the trajectories of its outcome. We present a review of relevant literature on categorical versus dimensional perspectives on psychopathology, with special reference to early signs, its relationship with other patient- and system-related characteristics, and the status and determinants of functional outcome and quality of life. The findings from longitudinal studies of the dimensional psychopathology of first-episode psychosis suggest continuity of some psychopathological dimensions from premorbid through prodromal to post-onset phases of psychosis and some aspects of longer-term course. Short-term functional outcome improves after treatment of the first episode, but longer-term outcome remains relatively poor for a substantial proportion of patients and is associated with preadolescent onset, poor premorbid adjustment, poor cognitive functioning, cerebral asymmetry, and negative symptoms during prodromal and post-onset phases. Poor quality of life is related to residual psychopathology, long delays in treatment, and poor premorbid adjustment. The potential effects of improved treatment and/or early intervention on functional outcome and quality of life have not been adequately examined, nor have the interrelationships between predictors and the underlying processes involved in determining variations in outcome. Studies of functional outcome still lack the rigor of operational definitions, choice of specific instruments for measurement, and use of large enough samples to generate meaningful results.

Key words: outcome/first episode/psychosis/functional

Introduction

Inconsistency in findings from a large number of studies of etiology, pathophysiology, and outcome in schizophrenia may partly be explained by the extreme heterogeneity of the schizophrenia syndrome. While a great deal of consistency has been brought to bear on the diagnostic criteria used for defining schizophrenia (e.g., DSM-III/DSM-IV), such definition of the phenotype of schizophrenia is based mostly on convergent validity (agreement between expert raters) and variable degree of consistency in findings on specific risk factors, brain abnormalities, and prediction of outcome. Subjects included in research are generally selected on the basis of cross-sectionally determined diagnosis with an assumption of consistency across studies and over time in defining the syndrome.[1] Testing out such assumptions is likely to be aided by examining psychopathology over time, starting with the first episode.

Increasingly the effect of the illness and its treatment on patients' and their families' quality of life and whether patients can return to a productive level of functioning in the community have also begun to receive well-deserved research attention. This has been stimulated in large part by efforts of consumer and family advocates who face the effects of the illness in their daily lives. Whether the large number of studies carried out in the early phase of schizophrenia in the last couple of decades has improved our knowledge about psychopathology and outcome remains to be determined. In this review we will focus on aspects of clinical psychopathology, functional outcome, and quality of life as they relate to the first episode of psychosis.

Method

A review of the relevant literature was conducted using the following keywords: *first-episode psychosis, clinical presentation, psychopathology, symptoms, course, outcome, quality of life, follow-up study, employment*, and *functional outcome*. The literature review was conducted using Medline and Psych Abstracts. We selected studies or reviews from those published between 1985 and 2005 and which involved patient populations presenting with a first episode of nonaffective psychosis. We included only those studies in which the subjects had received a diagnosis of a psychotic disorder according to DSM, International Classification of Disease, or Research

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Diagnostic Criteria. We included studies that involved patients with first-episode schizophrenia spectrum psychotic disorders with or without other psychotic disorders included in the sample. We did not include studies of patients described as "prodromal" or at "ultrahigh risk." Additional studies were reviewed through cross-referencing with publications identified through the search. We have used the term *schizophrenia spectrum psychosis* (SSP) to include schizophrenia, schizophreniform psychosis, and schizoaffective disorder, while the term *nonaffective psychosis* is used to include, in addition, delusional disorders and psychosis not otherwise specified.

Psychopathology of First-Episode Nonaffective Psychosis

Studies of psychopathology based on first-episode psychosis (FEP) populations have the advantage of examining large samples of patients who, while diagnostically heterogeneous, share some common elements in psychopathology. Longitudinal follow-up of these samples allows us to examine the emergence of more homogenous groups. These profiles may cut across diagnostic groups but provide more valid correlates of the psychopathological phenotypes. Although major distinctions in diagnosis can be made relatively early on between nonaffective and affective psychoses, some degree of overlap becomes apparent only over time. In this section we will include a brief examination of categorical versus dimensional approaches to psychopathology; the development of such dimensions in the early pre-psychotic phase; and the influence of patient, illness, or other variables (e.g., premorbid adjustment, age of onset, gender, duration of untreated illness, and substance abuse) on psychopathology.

Categorical Versus Dimensional Approach to Psychopathology

Reliance on a cross-sectional diagnosis at initial assessment in the context of shifts in diagnosis over time has been regarded as a limitation of past studies.[1] However, most, but not all, studies report significant stability of diagnosis over time as well as high predictive validity for long-term outcome if the initial diagnosis is schizophrenia.[2–5] Including patients with multiple episodes and using the 6-month criterion of symptoms for diagnosis of schizophrenia (DSM-III-R)[6(p567)] increases specificity but reduces sensitivity for diagnosis of schizophrenia. Longitudinal studies of cohorts of FEP patients also suggest relative stability of diagnosis of schizophrenia but not for schizophreniform disorder.[7] In samples of people with FEP the proportion of patients with diagnosis of schizophreniform disorder is likely to vary with the distribution of the duration of untreated psychosis (DUP), especially if there have been active measures taken to reduce DUP. Inclusion or exclusion of patients with comorbid substance abuse is also likely to influence the diagnostic composition at initial assessment and shifts in diagnoses over time.

It has been suggested that schizophrenia tends to be underdiagnosed in clinical settings.[8] A low level of agreement (Kappa 0.55) between clinical and research diagnoses has been confirmed in a recent study of FEP.[9] Gelber et al. have found that within a sample of first-episode psychoses the odds of diagnosis of schizophrenia are increased with certain patient and illness characteristics such as a longer DUP, being African American, higher levels of both positive and negative symptoms, and worse levels of quality of life and premorbid adjustment.[10] Whether the relatively modest level of discrimination at initial assessment is likely to affect treatment is largely unknown and may not substantially influence initial treatment as suggested by most clinical guidelines.[11–12]

A categorical approach to understanding psychopathology has been criticized for failing to address heterogeneity in schizophrenia and related disorders. In recent years considerable progress has been made in promoting a dimensional perspective for understanding psychopathology based on factor analytic studies, although the number of dimensions identified has varied across studies depending on the nature of the instruments used and the heterogeneity of the patients included.[13–20] Studying representative or incidence samples of functional psychoses during their first episode and followed prospectively without a priori assumptions about diagnostic subgroups may be more informative[21] as psychopathology dimensions may evolve over time.[22–26] Studies of FEP have largely confirmed a dimensional structure of psychosis, even though the number of dimensions reported has varied across studies.[27–31]

Although there is limited evidence for validation of the dimensional approach through association with differential outcome[30] and neurobiological correlates,[32] these have not been explored in first-episode (FE) samples. If we are to understand these phenotypes beyond simply descriptive phenomenology, validation of each dimension over time and association with outcome and neurobiological correlates will be required. Further, longitudinal studies will need to tease out the initial heterogeneity by identifying subgroups with distinct longitudinal patterns of respective dimensions, pathophysiologies, and outcome. This may involve a combination of factor analytic techniques and clustering methods so that clusters of patients with distinct psychopathological features can be identified and followed up. Shtasel et al. have applied such an approach to a sample of 37 FE and 70 chronic schizophrenia patients using a combination of several rating scales (Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms, Brief Psychiatric Rating Scale, Hamilton Rating Scale for Depression).[33] All FE patients met criteria for schizophrenia at 6-month follow-up assessment.

Four factors representing negative symptoms, positive formal thought disorder and bizarre behavior, hallucinations and Schneiderian delusions, and grandiosity and paranoia were identified. Patterns in FE and chronic patients were similar, although FE patients showed lower scores on the thought disorder factor than the chronic patients. Through applying factor scores to the whole sample, 3 clusters of patients were identified in *both* FE and chronic samples. Cluster 1 represents patients with prominent negative symptoms and moderate thought disorder, delusions, and hallucinations; Cluster 2 patients had mainly thought disorder and paranoia/grandiosity; and Cluster 3 patients had high levels of hallucinations and delusions. Compared to chronic patients FE patients were reported to show lower levels of thought disorder and higher levels of delusion within Cluster 1 and higher levels of hostility and avolition and lower levels of thought disorder in Cluster 2. No differences were reported in Cluster 3. While this approach suggests a more comprehensive method of investigating psychopathology, the lack of differences between FEP and chronic patients may be explained by the FEP sample being very small and diagnostically restricted a priori to schizophrenia and the comparison sample being limited to patients who could be drug free for long periods.

Additional support for a dimensional model of the psychopathology of psychotic disorders comes from investigations that have examined incidence, prevalence, and course of psychotic or psychosis-like phenomena in the general population.[34–36] The results of these studies suggest that delusional ideation and isolated hallucinations are relatively prevalent in the general population (15–16%) and that they constitute a significant risk factor for the development of diagnosable psychotic disorders.[37–38] The factor structure of symptoms reported from such community samples also suggests at least 3 distinct dimensions in congruence with what has been reported in some clinical populations of psychosis.[13–14, 27–28] These studies suggest a continuum of phenomena ranging from psychosis-like experiences, variable disorganization of thought process, disorders of affect, and negative symptom-like behavior to fully formed psychotic symptoms with additional dysfunctions in other domains.[35, 39] This model is not inconsistent with either a polygenetic[40] or a stress-vulnerability[41–43] model of understanding psychotic disorders. The above brief review would suggest that pursuing investigations of FEP from a dimensional perspective may assist us in identifying longitudinally more durable clinical phenotypes for further examination of etiology and pathophysiology.

Negative Symptoms in First-Episode Psychosis

One of the challenges of investigating psychopathology in FEP is the status of negative symptoms and their relevance to long-term outcome. Negative symptoms form a particularly important dimension of psychopathology because of their association with poor functional outcome,[44–46] a stronger relationship with cognitive functions[46–50] than that seen with positive symptoms, and a relatively poor response even to novel antipsychotic medications.[51–53] Factor analytic studies, in general, have identified negative symptoms as a single dimension. Most of these studies have not separated primary from secondary negative symptoms, a necessary distinction as suggested by longer-term studies,[54–55] nor has the longer-term progression of negative symptoms following the first episode been examined. During a first episode of psychosis negative symptoms that meet criteria for deficit[54] or primary negative symptoms (not influenced by depression or extrapyramidal symptoms) show a relatively low prevalence (19–27%)[56–57] depending on the definition applied and may consist of 2 distinct dimensions: alogia/affective flattening and anhedonia/apathy.[57] In an examination of the progression of negative symptoms in a large sample of FEP patients over 1 year, only 23% showed persistent primary negative symptoms at 1 year.[58] Patients with persistent negative symptoms were characterized by high levels of flat affect at initial evaluation, very long DUP, poor premorbid adjustment, and a trend for lower levels of performance on all domains of cognitive functioning. Edwards et al. have also shown that negative symptoms during FEP are unstable and that enduring negative symptoms are related to long DUP.[59]

It has been suggested that deficit syndrome may represent a distinct disease entity with underlying pathophysiology different from that of nondeficit schizophrenia.[54–55, 60] It is likely that patients who show persistent negative symptoms within the first year following the initiation of treatment have the same underlying pathophysiology as those who later meet criteria for deficit syndrome. Future investigations will need to identify neuroanatomical and/or functional characteristics accompanying early primary negative symptoms in subgroups of patients with FEP in order to attempt different approaches to treatment early in the course of illness.

Early Signs of Schizophrenia

Psychotic symptoms in schizophrenia spectrum disorders are almost invariably preceded by nonspecific changes in behavior and emotions.[61–67] More recently systematic investigations based on samples of FEP have confirmed that during the pre-psychotic phase of the illness most patients experience 1 or more nonspecific symptoms such as sleep disturbance, anxiety, irritability, depressed mood, decline in social relations and personal functioning, suspiciousness, loss of motivation, and apathy.[65, 68–71] There is remarkable agreement about the most frequent pre-psychotic early signs reported by patients with FEP.[65, 68–70] In a recent study FEP patients reported a number of pre-psychotic symptoms (mean 7.5), with the

frequency of individual symptoms varying from low (10% or less) for symptoms such as inappropriate affect, catatonia, and passivity experiences to high (40–75%) for symptoms such as impaired role functioning, depression, anxiety, social withdrawal, odd bizarre ideas, and suspiciousness.[71] Similar results regarding the frequency and type of symptoms are reported by Gourzis et al.,[69] with a median of 8 symptoms in a sample of 100 FE schizophrenia patients in comparison with a median of 0 in a control sample. While the term *prodrome* is commonly used to describe such pre-psychotic symptoms, these early symptoms can only be called ''prodromal'' retrospectively if they are reported to have preceded the first psychotic episode, and as such they have limited predictive value for the onset of psychosis (low specificity). However, symptoms such as odd bizarre ideas and suspiciousness may have a higher specificity for psychosis, particularly if they occur more proximally to the onset of psychosis.[69]

Exploration of early signs during the pre-psychotic phase is important for informing us better about the feasibility of preventive interventions during this phase.[72–73] This line of investigation has required that pre-psychotic symptoms have greater specificity, that they be relatively proximal to the onset of psychosis, and that the risk conferred by the presence of such symptoms be of sufficient magnitude and imminent enough to justify interventions. Klosterkotter et al.[74] report a study assessing the predictive value of ''prodromal'' symptoms as defined by Huber.[75] From an original sample of 385 psychiatric patients, who had sought treatment for disorders other than psychosis and been assessed for the presence of ''prodromal'' symptoms with the Bonn Scale for Assessment of Basic Symptoms (BSABS),[75] 160 were reassessed after a mean of 9.6 years. A correct prediction of schizophrenia with a probability of 70% and exclusion of schizophrenia with a probability of 96% based on the presence or absence of ''prodromal'' symptoms, respectively, was made. Of the 5 hierarchical clusters identified to make up the BSABS,[76] the cluster indicating disturbance in thought, language, perception, and motor skills had the highest predictive value.[74]

Prodromal symptoms described in the BSABS have been incorporated in several other measures of early signs of psychotic disorders (e.g., the Interview for Retrospective Examination of Onset of Schizophrenia)[77] and in more recent work identifying individuals at ultrahigh risk for psychosis.[67, 78–79] For the latter, a combination of state (e.g., subthreshold symptoms) and trait (family history of psychosis) characteristics usually confers a 25–40% risk of conversion to psychosis within 1 year of follow-up.[80–81] The observation of a relatively variable rate of conversion to a clinically diagnosed psychotic disorder in this group and the possibility of that transition from psychotic experiences, as a more widely distributed phenomenon, to psychosis as a clinical disorder likely require several additional factors that would further support a dimensional perspective for understanding psychopathology.

A second line of investigation of ''early signs'' has involved an examination of their continuity over time and through the transition to psychosis and recovery.[69] The phenomenology of early signs of schizophrenia is likely to be similar to that of residual symptoms following treatment,[82] and patterns of symptoms from the pre-psychotic phase through onset and over the course of the disorder may be potentially significant.[69, 83–84] Norman et al. recently reported a 5-factor structure for pre-psychotic symptoms based on a principal component factor analysis in a sample of 96 FE schizophrenia spectrum psychoses.[71] The results show some continuity in content between a pre-psychosis symptom factor and subsequent symptom dimensions after the onset of psychosis. For example, a factor reflecting impaired role functioning, social withdrawal, and decreased energy was related to high scores on negative symptoms at the presentation of FEP. Further, aspects of pre-psychotic symptoms may also have a prognostic value. For example, in the same study, a factor representing changes in energy level, sleep patterns, and appetite and restlessness was predictive of greater improvement in psychotic symptoms at the end of 1 year of treatment, independent of the level of psychotic symptoms prior to treatment, gender, and diagnosis (schizophrenia versus schizoaffective disorder).[71] The authors suggest that psychobiological changes may reflect the contribution of some underlying mood changes to the onset of psychosis, conferring a better prognosis. Another report, on the other hand, fails to find early signs of depression to be predictive of course of psychotic symptoms.[84] The latter study reports on subjective mood changes that may reflect cognitive changes involved in the process of developing psychosis rather than biological shifts associated with depression.

In a prospective study of 94 patients considered to be in a putatively prodromal state (ultrahigh risk) for a psychotic disorder, Hawkins et al.[82] conducted a factor analysis of ratings on items on the Scale of Prodromal Symptoms.[85] The authors report a 3-factor structure made up of a negative symptom factor that includes disorganization and odd behavior, a general dysphoria factor (sleep problems, dysphoric mood, etc.), and a positive symptom factor (unusual thought content, suspiciousness, and perceptual abnormalities), suggesting a continuity with dimensions of psychopathology seen in established FEP. Some degree of congruence seen in the studies by Norman et al.[71] and Hawkins et al.[82] regarding early signs of psychotic disorders, despite differences in methodology and stage of the illness at the time of assessment, suggests a continuity of symptom dimensions from very early stages prior to the onset of psychosis, albeit with limited specificity for any particular sign.

Premorbid Characteristics and Psychopathology of First-Episode Psychosis

An additional line of investigations has examined the relationship between premorbid characteristics and psychopathology of FEP patients. Poor premorbid adjustment in social and academic domains during childhood and early adolescence in schizophrenia patients in comparison to nonpsychiatric controls has been considered supportive of a neurodevelopmental model.[86–89] While studies of chronically ill patients have provided stronger evidence for a relationship between poor premorbid adjustment and negative compared to positive symptoms,[90–93] those examining relationships between psychopathological dimensions in FEP and patterns of premorbid functioning have confirmed a significant association between poor premorbid adjustment and negative symptoms at presentation of FEP.[94–95] Investigations of premorbid functioning in FEP patients have the advantage of greater reliability of recall of events and patterns of behavior due to their greater proximity to the index episode of the disorder; better access to family members, especially parents, for verification of childhood behavior; and lack of contamination from long periods of hospitalization and treatment.

In a large sample ($N = 535$) of FE schizophrenia spectrum psychoses Rabinowitz et al.[96] examined the relationship between 3 patterns (stable good, stable poor, and deteriorating)[97] of premorbid adjustment using the Premorbid Adjustment Scale (PAS)[98] and symptom severity and cognitive functions. Patients with ''stable good'' (47.5%) premorbid adjustment had lower scores on the negative syndrome and general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS) compared to those with ''stable poor'' (37.3%) and ''deteriorating'' (15.2%) adjustment types. They also scored better on several cognitive measures. Results of a discriminant function analysis show that the negative syndrome subscale of PANSS and the ''category'' section of the verbal fluency test significantly discriminate among the 3 premorbid adjustment groups. The culturally and linguistically heterogeneous nature of this international sample, involvement of multiple raters, previous treatment with antipsychotic medication for up to 3 months, and variable access to sources of information other than the patient in the assessment of premorbid adjustment may limit generalization of these findings. However, in a more homogenous sample of 113 subjects with FE SSP (75% schizophrenia) from a defined catchment area with less than 1 month prior exposure to antipsychotic medications, Norman et al. observed a modest but significant relationship between higher (worse) scores on PAS and higher ratings on the psychomotor poverty dimension at first assessment ($r = .22$, $p < .05$) and 1 year later ($r = .24$, $p < .01$), as well as with poor functioning on most cognitive domains (ranging from $r = .22$ for processing speed to $r = .52$ for verbal IQ).[99] Of particular note is that the relationship between cognitive functions and premorbid adjustment is almost entirely accounted for by adjustment on the academic domain, and this association extends to all cognitive measures except visual memory. Applying the Haas and Sweeney[97] method of classifying premorbid adjustment, Norman et al.[99] report distribution of PAS groupings remarkably similar to those of the Rabinowitz study. The ''stable good'' group showed lower levels of negative symptoms compared to the other 2 groups (''stable poor'' and ''deteriorating''), with no differences between the latter 2 groups, and the differences in negative symptoms were accounted for mostly by premorbid adjustment on the social domain. On most cognitive measures the ''stable poor'' premorbid adjustment group showed the worst performance, and these differences were entirely based on premorbid adjustment in the academic domain.[99]

Cuesta et al.[100] have examined more stable personality characteristics in a sample of 94 FEP patients recruited from consecutive admissions to a hospital within a defined catchment area using the Premorbid Assessment Schedule[101–102] for ratings of personality dimensions by a rater blind to psychopathological assessments. They report the negative symptom dimension to be associated with higher scores on schizoid ($r = .42$, $p < .001$), passive-dependent ($r = .27$, $p < .01$), and schizotypical ($r = .20$, $p < .05$) personality dimensions. Relatively modest correlations are also reported between sociopathic and passive-dependent personality dimensions and the hostility/suspiciousness symptom dimension ($r = .29$/$r = .27$, respectively, $p < .01$). In the schizophrenia subgroup significant associations were reported between schizotypy and the positive symptom dimension ($r = .42$, $p < .01$). Relationship with cognitive measures was not examined. There is likely some consistency in the results of the above studies despite differences in methodology. For example, the schizoid dimension[100] incorporates behavior patterns that would be rated as poor social adjustment on the Premorbid Adjustment Scale,[96, 99] and both show similarly strong associations with negative symptoms.

In the absence of any relationship reported between positive symptoms of psychosis and premorbid adjustment it is likely that the relationship with negative symptoms is independent of the influence of positive symptoms. Continuously poor social adjustment during childhood and adolescence may be a vulnerability marker for greater propensity toward negative symptoms, while lower academic performance during childhood and early adolescence is likely to be a marker for poor cognitive functions. Negative symptoms and cognition, while modestly correlated, are relatively independent constructs and may represent different neural pathways. These findings also support the existence of a subgroup of FE schizophrenia spectrum psychoses patients in whom the origins

of the disorder are more clearly related to neurodevelopmental problems. On the other hand, the subgroup that starts with a relatively normal premorbid social and academic development but later shows deterioration during adolescence, present with less severe negative symptoms and more intact cognitive functions, may suggest the existence of a neurodegenerative process beginning much before the onset of psychosis. In a later section we will examine whether these differences in premorbid functioning have an impact on the course of the illness.

Serious Behavioral Problems Associated With First-Episode Psychosis

Violence and suicide are some of the gravest consequences of psychotic disorders. Such behavioral characteristics are, therefore, important targets for intervention during FEP and for prevention over the course of illness. Studies of FEP have generally shown high rates (20–30%) of violence and/or verbal aggression prior to or at the time of initial presentation and lower rates (7–16%) in the weeks subsequent to hospital admission or contact with mental health services.[103–106] Violence and aggression prior to assessment have been reported to be significantly associated with drug misuse and involuntary status on admission to hospital, and violence after contact with mental health service has been associated with poor insight and precontact violence.[105] Suicide is well known to be the leading cause of excess mortality in schizophrenic disorders especially during the first few years after onset.[107] Patients with FEP present with high rates of suicidal behavior (11–26%),[106, 108–110] and this is significantly associated with drug misuse ($p < .03$), especially polysubstance use.[108] Predictors of suicidal behavior over the subsequent 2 years have been reported to include a lifetime history of suicidal behavior, lower positive symptom scores, longer duration of psychotic symptoms, longer duration of first admission, continuing substance misuse, and higher risk of readmission to hospital.[111] Treatment services for FEP may need to pay special attention to problems of violence and suicidal behavior.

Relationship of Symptoms to Other Patient Characteristics

A number of characteristics related to patients, the treatment system, and variations in expression of the illness may contribute to variations in the nature and severity of psychopathology at the time of first presentation.

Gender and Psychopathology. In general, research on gender differences has suggested that males have an earlier onset, a poorer premorbid adjustment, a higher level of negative symptoms, and a lower frequency of affective symptoms.[112–113] Whether the differences in psychopathology are accounted for by gender, differences in age of onset, or both remains largely unresolved. Examination of gender differences in FEP has produced mixed results. Most recent study samples of FEP have included a predominance of male subjects, especially those that have reported exclusively on nonaffective psychosis.[114–116] Whether this reflects a true sex difference in incidence rates of schizophrenia spectrum psychosis or is an artifact of sampling and help-seeking behavior is beyond the scope of this article. Some studies have reported female patients to present with a lower level of negative symptoms,[59] while others have failed to find any such difference.[57, 117] Studies in more chronically ill patients have generally reported a higher frequency of primary and sustained negative symptoms in males.[54] On the other hand, female schizophrenia patients have been reported to show greater levels of dysphoric and affective symptoms,[118] and this finding has recently been reported to exist even during the pre-psychotic phase as part of the early signs.[71]

While gender differences have been reported consistently in the level of premorbid adjustment in FEP samples,[96, 99] results on the nature of these differences are not entirely consistent. For example, Rabinowitz et al. report that compared to female subjects a much higher proportion of male FEP subjects showed the ''deteriorating'' type of premorbid adjustment (39 versus 9%), and a smaller proportion showed ''stable good'' (44 versus 57%) and ''stable poor'' (18 versus 34%).[96] Similar findings of progressive decline in premorbid functioning in male FEP patients are reported by Strous et al.[119] Norman et al., on the other hand, report that male subjects had a higher proportion with the ''stable poor'' (28.4 versus 8%) and ''deteriorating'' (40 versus 28%) type of premorbid adjustment and a lower proportion (32 versus 64%) with ''stable good'' adjustment.[99] These differences in results have implications for interpretation of the gender differences reported. The 2 earlier studies[96, 119] would suggest a progressive deterioration in male patients (neurodegenerative), while the later study[99] would suggest a combination of neurodevelopmental and early neurodegenerative basis to SSP in males.

Early Age of Onset and Psychopathology. Onset of schizophrenia especially during childhood and early adolescence has often been associated with a more severe form of illness and poor outcome. Notwithstanding some uncertainty in diagnosing schizophrenia during childhood, reported especially in earlier studies,[120–121] most studies have confirmed a worse outcome for schizophrenia diagnosed in childhood or early adolescence compared to other psychotic disorders.[122] A more recent 11-year follow-up study of early adolescent onset psychosis (age 10–17) into adulthood reports a high degree of consistency for the initial diagnosis through adulthood for both schizophrenia (80.4%) and affective psychosis (82.6%) and relatively low consistency for schizoaffective psychosis (33.3%).[123] The relative instability of diagnosis

reported in earlier studies[124] may reflect less differentiated presentations of psychoses during childhood, and the differences may be more quantitative than qualitative in relation to adolescent-onset psychosis.[125–126] A greater overlap with affective symptoms[126–128] and a higher frequency of behavior problems and dysphoria in adolescent onset may also account for the diagnostic instability in this age group. Some studies of childhood and adolescent psychosis have reported psychopathological domains similar to the ones in adult FEP patients.[129]

A recent comparison of all consecutively assessed FEP patients ($N = 201$) in a defined catchment area with an adolescent onset (15–18 years) and those with an adult onset (19–30 years) showed that 40.8% of patients had their onset of psychosis between the ages of 15 and 19 years; the adolescent-onset group had significantly longer DUP, modestly worse scores on the Premorbid Assessment Scale, a higher level of bizarre behavior and affective flattening, and a higher frequency of negative symptoms.[130] Younger age of onset has also been associated with greater level and number of Schneiderian first-rank symptoms with no specificity for diagnosis of schizophrenia.[131]

A longitudinal cohort study of children ($n = 761$) has shown that self-reported psychotic symptoms (hallucinations and delusions) at age 11 are highly predictive of schizophreniform psychosis in adulthood (Odds ratio 16.4, 95% CI 3.9–67.8), with an attributable specific risk of 42% for schizophreniform psychosis at age 26.[37] Persistent voices heard in childhood tend to continue in a significant proportion, and this is associated with a greater severity of voices, a higher level of anxiety/depression, a lack of triggers, and revealing the experience to more people.[132] These findings from prospective studies of children suggest that psychosis-like phenomena, while not uncommon in childhood, may have a role in causing future psychotic disorders in the presence of other risk or mediating factors.

Delay in Treatment and Psychopathology. Delay in treatment, expressed as DUP and assessed as the time of onset of psychotic symptoms to the time of adequate antipsychotic treatment, has been investigated very extensively in studies of FEP. Most have examined the relationship of DUP with psychopathology, mostly as a possible confound of the primary hypothesized relationship between DUP and outcome. The majority of studies have failed to find a significant relationship between age of onset and DUP,[97, 130, 133–137] with a couple of exceptions.[130, 138] Ho et al. have used a very broad measure of age of onset,[138] while Ballageer et al. have compared adolescent onset (15–18 years) with adult onset (19–30).[130] The most consistent finding is a significant relationship between longer DUP and a higher level of negative and deficit symptoms.[59, 136, 139] A closer examination of this relationship has revealed that the positive correlation between negative symptoms and DUP is accounted for almost entirely by only 1 (apathy/anhedonia) of the dimensions of negative symptoms and that a second dimension (alogia/affective flattening) shows no relationship with DUP.[57] It is of interest to note that apathy/anhedonia are highly correlated with positive (psychotic) symptoms, while alogia/affective flattening are not. There is also some evidence that shorter DUP may be correlated with the acute onset of psychosis;[133, 136] however, there is no definitive method to estimate acuity of onset. Findings related to DUP need to be interpreted with caution because of considerable variation in the methods of assessment and definition of DUP used.[140]

Substance Abuse and Psychopathology of First-Episode Psychosis. While it is beyond the scope of this review to explore issues of comorbidity in any detail, substance abuse is of particular significance by reason of the high prevalence of such behavior in this patient population and its potential effect on psychopathology.[141–145] Alcohol and cannabis appear to be the most common drugs abused, and most have reported that substance abuse usually predates the onset of psychotic symptoms,[143, 144, 146] especially in the case of cannabis. The onset of drug abuse precedes the onset of negative and positive symptoms, while the onset of alcohol abuse occurs at the same time as the onset of negative symptoms and significantly prior to first psychotic symptoms.[141] Few differences in symptoms have been reported between substance-abusing and non-substance-abusing FEP patients, except for increased antisocial behavior and thought disturbance[141, 143] and better premorbid adjustment and higher cognitive functioning[142] in substance-abusing FEP patients.

To summarize, studies in the psychopathology of FEP suggest that there is greater consistency in diagnosis over time for schizophrenia than for other nonaffective psychoses. A dimensional structure of psychopathology may provide more meaningful phenotypes of a heterogeneous disorder through showing greater longitudinal consistency both prior to and after the onset of the psychotic syndrome and through a differential relationship with more stable characteristics such as premorbid adjustment. Finally, a number of characteristics associated with the illness, the patient, and the system of care may have significant effects on psychopathology in FEP.

Functional Outcome in First-Episode Psychosis

Psychopathology is important for understanding the nature of psychosis and may assist in predicting outcome. For the individual patient, his or her family, and, increasingly, the clinicians and policy-making community, occupational and social functioning and the person's quality of life may be even more important as a measure of the impact of the illness and/or its treatment. Numerous

studies have examined longitudinal outcome in schizophrenia,[147–148] and there have been many reviews of outcome studies including some meta-analyses.[149] Most of these studies have used "prevalence" samples that introduce a bias from the overinclusion of chronically ill patients. Longitudinal studies of cohorts of patients presenting with their first episode of illness are likely to provide more informative data regarding the course and outcome trajectories of subgroups contained within the cohorts. In a previous review of studies of first-admission cohorts Ram et al. identify several limitations to this first generation of prospective outcome studies.[1] These include small sample sizes from single sites, inclusion of only patients with a diagnosis of schizophrenia, exclusion of patients with concurrent substance abuse, reliance on cross-sectionally determined diagnosis, short follow-up periods, and inadequate data on length of untreated illness and subsequent treatment experience. In addition, follow-up studies have not usually separated clinical from functional outcome.

Despite these methodological limitations of earlier cohort studies, their results confirm a variable outcome depending on the length of follow-up and suggest that a larger proportion of first-admission cohorts have a good outcome compared to previous "prevalence" samples. The overall outcome, however, still remains poor, with high rates of relapse. Variables such as early neuroleptic treatment and shorter duration of outcome have been judged to be favorable for outcome.[1]

Over the past decade and a half a great deal of enthusiasm has been generated about the possibility of improving outcome in schizophrenia and related nonaffective psychotic disorders.[150–153] In addition to the purported improved response of positive and negative symptoms and cognitive functions with the use of novel antipsychotic medications and the demonstrated efficacy of psychosocial interventions, such enthusiasm is, in part, based on the evidence of a significant relationship between DUP and clinical and functional outcome, at least in the short term,[51, 133, 135, 150, 154–159] although not all studies have supported these findings.[160–163] This has in turn generated enthusiasm about the potential of reducing DUP through early case detection and intervention and thereby improving outcome.[164–166] The notion of there being a "critical period" of 3 to 5 years after onset of psychosis when interventions are likely to have the maximum effect[167] and when future trajectories of functional outcome may be set[168] has provided further support to the idea of early intervention. The potential for improving outcome through simply an earlier timing of interventions is likely to be limited unless combined with improved treatment that is more suited to the earlier phase of illness and to a younger patient population.[169–171] It is in these contexts that the most recent studies examining outcome in first-episode schizophrenia spectrum psychotic disorders will be reviewed.

In examining the question of whether our knowledge about functional outcome in these disorders has improved as a result of the new wave of studies of FE samples we have chosen to separate "functional outcome" from outcome in "quality of life." For the former we have included studies that examine outcome on community and social functioning, employment/education, and financial and housing independence. Under "quality of life" we have included studies that specifically examine the construct of "quality of life." We recognize that there is considerable overlap between these 2 constructs and have made relevant comments for clarification when required.

We identified a number of studies that report on at least 1 aspect of functional outcome as defined above with at least 1 year of follow-up. The length of follow-up ranged from 1 to 15 years, with the majority of studies reporting 1- to 2-year follow-ups. Some long-term studies (10–15 years) fail to provide details of social and occupational outcome but reveal a significantly worse outcome for a sample of FEP patients in the Netherlands than for a sample in India on measures of suicide, rates of hospitalization, and employment.[172–173]

Occupational Adjustment or Role Functioning

There are few studies that were designed specifically to examine outcome on employment or return to educational pursuits. Several studies, however, include some measure of vocational adjustment, and they are summarized in Table 1. These studies vary greatly in the method used for assessing role functioning, definition of role functioning, length of follow-up, inclusion of FEP other than schizophrenia, sample size, and reporting of treatment experience and other patient characteristics. These differences explain the wide range of the proportions of patients considered to be meeting standards for proper role functioning. Only 3 studies report whether patients were financially dependent on state or other sources, although the availability of such benefits is likely to vary across different systems of care.[46, 174–175] Some studies report data on employment and other aspects of role functioning (student, homemaking) at follow-up without reporting data at entry,[46] while others provide incomplete information making it difficult to judge change in role functioning at follow-up.[176–177] For example, de Haan et al. report mean number of hours worked or at school but do not provide data on the proportion of patients engaged in such activities.[116] Addington et al. report that 28 of the 76 patients unemployed at entry were either employed or students at 12-month follow-up, while an almost equal proportion (23/101) shifted from being employed to being unemployed at follow-up, so that there was only a net gain of 5 patients in employment.[114] Tirupati et al. report a relatively high rate of employment with a gain of 14% over the course of 1 year of treatment for a sample of patients in India who had been untreated

Table 1. Vocational Outcome—Follow-up Studies of First-Episode Psychosis

Reference	*N*	Length of Follow-up (years)	Diagnosis (and % S)	Mean Age	% Male	Maximum Prior Antipsychotic Use	Outcome Measures	% Adequate Role Functioning	% Financially Dependent
Addington, Young, & Addington, 2003	177	1	SSP (74%)	24.5	66	12 weeks	general (and QLS)	59.9	–
Tirupati, Rangaswamy, & Raman, 2004	49	1	S (100%)	18–40	62	–	general	51	–
Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998	49	2	S (100%)	23.9	64	12 weeks (median)	GSA; GAS	40	64
Lehtinen, Aaltonen, Koffert, Rakkolainen, & Syvalahti, 2000	106	2	NAP	29.4	56.6	?	general; GAS	32	53
Linszen, Dingemans, & Lenior, 2001	71	5	SSP (55%)	19.3[a]	48	?	WHO-LCS	(16.6)[b]	–
Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004	118	5	SSP (70%)	25.2	52	12 weeks	SAS-II	25.5[c]	–
de Haan, Linszen, Lenior, de Win, & Gorsira, 2003	88	6	mixed (84%)	19[a]	77	?	WHO-LCS modified	(3.4–7.2)[b]	–
Stirling, White, Lewis, et al., 2003	49/112	10	FEP (85%)	26.3	56	?	WHO-LCS	8	66

Note: S = schizophrenia, SSP = schizophrenia spectrum psychoses, NAP = nonaffective psychosis, FEP = first-episode psychosis, QLS = Quality of Life Scale, GSA = Global Social Adjustment (Psych-Base [Psychiatric symptoms you currently have: Baseline version] and Psych-Up [Longitudinal follow-up version of the Psych-Base]), GAS = Global Assessment Scale, WHO-LCS = World Health Organization Life Chart Schedule,[179] SAS-II = Social Adjustment Scale II.
[a]Age of onset.
[b]Mean number of hours at work, school, or household duties.
[c]Includes vocational and social functioning under 1 category.

Table 2. Quality of Life in First-Episode Psychosis

Reference	Sample (*n*)	% Male	Mean Age	Assessment Tool	Comparative Sample	Dimensions of QOL Reported	Relations With Other Factors	Outcome
Shtasel, Gur, Gallacher, Heimberg, Cannon, & Gur, 1992	FEP 37 (S)	62	27.8	QLS	chronic S ($n = 70$)	yes	cluster of negative symptoms and thought disorder	–
Browne, Clarke, Gervin, Waddington, Larkin, & O'Callaghan, 2000	53 (SSP)	68	25.3[a]	QLS	no	no	DUP > 12 months; total PANSS scores (negative symptoms)	–
Priebe, Roeder-Wanner, & Kaiser, 2000	86 (SSP)	34	30.4	LQOLP	chronic S (long stay, $n = 76$; community sample, $n = 143$)	yes	–	limited improvement at 9 months
Malla, Norman, McLean, et al., 2004	130 (mixed) (68% SSP)	77	26.1	W-QoLS	no	yes	age of onset; DUP; premorbid adjustment; negative symptoms; prodromal symptoms	–
Sim, Mahendran, Siris, Heckers, & Chong, 2004	66 (SSP)	–	28.2	WHOQOL-Bref	no	yes	depressive syndrome	–
McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996	200 (mixed)	65	22.0	QLS	no	no	association with DUP	significant improvement at 1 year
Malla, Norman, McLean, & McIntosh, 2001	41 (mixed) (78% SSP)	88	25.6	W-QoLS	no	yes	no association with DUP	significant improvement at 1 year
Addington, Young, & Addington, 2003	177 (mixed)	67.2	24.5	QLS	yes (normal control, $n = 40$)	no	association with remission, level of negative symptoms; positive symptoms; no association with DUP	significant improvement at 1 year
Whitty, Browne, Clarke, et al., 2004	72 (SSP)	55	32.3	QLS; WHOQOL-Bref	no	yes	no	4-year follow-up sample but no baseline data

Note: QOL = quality of life, FEP = first-episode psychosis, S = schizophrenia, SSP = schizophrenia spectrum psychoses, QLS = Quality of Life Scale, LQOLP = Lancashire Quality of Life Profile, W-QoLS = Wisconsin Quality of Life Scale, WHOQOL-Bref = World Health Organization Quality of Life Scale—Brief version, DUP = duration of untreated psychosis, PANSS = Positive and Negative Syndrome Scale.
[a]Age of onset.

for many years.[177] In reporting a relatively low rate of "social/vocational recovery" at 5 years following initial assessment, Robinson et al. use stringent but operationally defined criteria.[178(p474)] The criteria have 3 components, including appropriate role function defined "as paid employment, attending school at least half-time or homemaker, performing that role adequately or better," and patients had to meet these criteria for 2 years prior to outcome assessment to be regarded as "recovered." This is 1 of the few studies using clearly defined criteria for role performance. Two other studies[175–176] use rating instruments and operational criteria derived from the World Health Organization Life Chart Schedule[179] for assessment of role functioning. Stirling et al. report very low rates of full employment and high rates (66%) of disability pension 10 years after initial assessment for 49 of an original sample of 112 FEP patients.[175]

Two studies provide no clear description of the treatment received by patients.[175, 177] Two other studies[46, 178] provide descriptions of pharmacotherapy only, while the rest either provide detailed descriptions of psychosocial interventions[116, 174, 176] or make reference to a published description of a comprehensive program.[114, 180] Results reported by Lehtinen et al. are based on a comparison of 2 treatment facilities with similar psychosocial approaches to treatment, but 1 used neuroleptic medication only if needed (57.1% patients received) while the other site used them in routine practice.[174] No differences are reported in vocational adjustment.

Most of these studies also examined factors associated with vocational performance, but the predictors examined vary, as do the methods used. Premorbid adjustment[114] and diagnosis of schizophrenia spectrum psychoses[174] were modestly ($p < .05$) associated with worse vocational performance at 1- and 2-year follow-ups, respectively. In 1 study negative symptoms at initial assessment were related modestly to occupational impairment but strongly to financial dependence, and impairment in household duties and psychotic symptoms were related to financial dependence at 2-year follow-up;[46] while in another study differences between employed and unemployed at 1 year were found only in relation to concurrent psychotic and negative symptoms as well as scores on the Quality of Life Scale (QLS).[114] Differences in patient characteristics (e.g., diagnosis), the variables examined, the methods used for measurement, and possibly psychosocial treatment may explain some of the variation in outcome. None of the studies reports a relationship between delay in treatment of psychosis and vocational outcome, with the exception of Tirupati et al.,[177] who report modestly higher rates of employment in those with 5 years or less of DUP compared to those with DUP longer than 5 years. De Haan et al. examined the relationship between occupational outcome and delay in psychosocial versus neuroleptic treatment and have found no such relationship.[116] However, none of the studies, including the latter, reports any specific efforts made at improving vocational assessment such as supported employment.[181]

In a 5-year outcome study a global measure of cognition and a measure of cortical asymmetry (magnetic resonance imaging) were reported to be the only predictors of adequate vocational functioning ($p < .0001$), explaining 23% of variance in outcome.[178] Another study has found concurrent poor performance on 2 measures of cognition (the Wisconsin Card Sorting Test and the picture arrangement subtest of the Wechsler Adult Intelligence Scale [WAIS]) and deterioration in picture completion (WAIS) and memory for design to be predictive of an outcome factor that includes vocational performance at 10 years after initial treatment.[175] These 2 studies suggest a link between neurobiological measures and vocational outcome. Variations in level of psychopathological dimensions (e.g., negative symptoms) and premorbid adjustment, which also show an association with vocational outcome, may be proxy markers of this relationship. The results reviewed above suggest that occupational outcome may be related more to longer-term trait characteristics and sustained impairments associated with psychotic disorders. In addition external factors such as availability of employment and impact of stigma remain largely unexplored. Earlier timing of intervention alone is unlikely to bring about improvement in occupational outcome, and it may be necessary to initiate specific interventions such as supported employment early in the course of illness for specific subgroups of FEP patients. As none of the studies controlled for specificity or adequacy of treatment interventions, no conclusions can be drawn on the effect of treatment interventions on functional outcome.

Outcome on Community and Social Functioning

Outcome on other measures of community functioning such as living arrangements, self-care, and social relations has been reported by some as part of a composite measure incorporating it with vocational outcome.[46, 178] These studies provide a detailed definition of the outcome measure and/or data on each individual element of the social and occupational outcome and examine their relationships with symptoms and premorbid adjustment[46] or cognition and brain morphology.[178] Ho et al. report a robust relationship between negative symptoms at admission with impairment in social relationships with friends and enjoyment of recreational activities at 2-year follow-up ($p < .01$), independent of any relationship with premorbid adjustment.[46] De Haan et al. have found time spent in hospital during the follow-up period to be related to the delay encountered in receiving psychosocial treatment and not DUP.[116] No such relationship was found with social outcome. Linszen et al. report a significant amount of dependence on parents during a 5-year

follow-up,[176] and this was related to longer DUP. However, they provide no data on the relationship between DUP and dependence on parents, and their sample was very young (<26 years). Tirupati et al. report good social outcome, based on family and nonfamilial relationships, in 35% of their sample, with no significant association between DUP and social outcome.[177]

Malla et al. specifically examined change in 2 separate dimensions of community functioning, social relations and activities of daily living, in a sample of 66 FEP patients (81.2% SSP disorders) 1 year after treatment in a comprehensive early intervention program.[158] The 2 domains of outcome were derived from the Provider version of the Wisconsin Quality of Life Scale (W-QoLS).[114] Assessment of daily activities, independent living, and social behavior in the W-QoLS are based on the Life Skills Profile,[182] and social relations are examined in relation to family, friends, and acquaintances. Results showed a significant improvement in both dimensions of community functioning ($p < .01$). Impaired daily life skills were associated with worse levels of premorbid adjustment during early adolescence, concurrent residual symptoms (positive and negative), and poor adherence to medication ($p < .002$–$.0001$) and explained 49% of variance in outcome. Impaired social relations, on the other hand, were associated with poor premorbid adjustment in early adolescence, psychomotor poverty at 1 year, working memory index at 1 year, and adherence to medication. Harrigan et al. have examined the impact of several predictors including premorbid adjustment and DUP on "functional outcome" at 1-year follow-up on a large sample of FEP ($n = 354$, 76% with nonaffective psychosis).[183] Functional outcome was defined by total scores on the Quality of Life Scale, and no separate scores were provided for subscales of QLS. They found that DUP, premorbid adjustment, diagnosis, gender, model of treatment, and duration of prodromal period all made independently significant contributions to variance in outcome on QLS scores and explained 21% of variance. The above review suggests that community and social functioning is influenced by a combination of more stable characteristics such as premorbid adjustment as well as characteristics associated with the illness and its treatment (e.g., residual symptoms, treatment model, and adherence to medication).

Functional Outcome in Childhood- and Adolescent-Onset Psychosis

Patients with an onset of psychosis in childhood and adolescence have been generally reported to have worse outcomes than those with adult onset.[184] Two recent studies of longer-term follow-up of FEP cohorts with onset in childhood or early adolescence have been identified.[185–186] Schmidt et al. report the functional outcomes of a cohort of 118 FE schizophrenia patients (age 11–18 years).[185] Outcome was measured as social disability using a modified version of the World Health Organization Disability Assessment Schedule,[187–188] and educational/occupational outcome was based on deviation from the expected (premorbid) level on average 7.2 years after initial treatment. Results indicate very low rates of independent living (16.5%) and occupational source of income (17.5%) and high rates of occupational impairment of at least moderate severity (44%) and financial dependence on parents (51.6%) or public assistance (30.9%). Both aspects of functional outcome were highly (inversely) correlated with level of social competence and the level of positive and negative symptoms at initial discharge from hospital, duration of the first episode, and total number of episodes during the follow-up period. A more recent study reports a 10-year (range 5–18) follow-up study of 81 patients with childhood- and adolescent-onset FEP, including schizophrenia, schizoaffective, bipolar, and depressive psychoses, with an average onset at 15.6 years (11.8–17.7).[186] Functional outcome was measured using the Global Assessment of Functioning, Strauss-Carpenter Scale,[189] and information regarding independent living and financial dependence. Results show that compared to those with affective psychosis, patients with schizophrenia or schizoaffective psychosis had high rates of poor to very poor global outcome (75 versus 26%), unemployment (48 versus 10%), lack of social contacts (42 versus 7%), disability pensions (85 versus 35%), and low scores on the Strauss-Carpenter Scale (8.9 versus 16.5). Poor outcome in the schizophrenia group was especially associated with positive family history of nonaffective psychosis. Long-term studies of schizophrenia spectrum psychosis with onset in childhood or adolescence largely confirm a poor outcome on a number of social and occupational measures.

Quality of Life in First-Episode Psychosis

In recent years, health-related quality of life (QOL) has come to be regarded as an important dimension of outcome in schizophrenia and other serious mental disorders.[44, 190–192] This interest may have been stimulated by an expectation related to the introduction of newer antipsychotic medications.[193–195] Consumers of mental health services have also felt increasingly empowered to expect and demand a better QOL.

The question about what should be incorporated in the concept of quality of life remains largely unresolved, although its subjective nature is generally regarded as central to the concept.[190] In measuring QOL there are 2 competing models.[196] Measures based on the "satisfaction model" tend to focus on the individual's satisfaction with different domains of life of personal significance and on an overall sense of well-being. Such measures are not necessarily disease specific. An alternative model based on a broader definition of QOL would incorporate levels

of functioning and social and material conditions in addition to satisfaction with life. Measures that have been used in research in QOL in psychiatric patients have involved either self-reports of a generic nature such as the 36-item Medical Outcome Study—Short Form,[197] the General Well Being Scale,[198–199] and the World Health Organization Quality of Life scale;[200] more disease-specific scales such as the Wisconsin Quality of Life Scale;[201] or alternatively more "objective" measures such as rating scales (e.g., the Quality of Life Scale,[202] Lehman Scale[203]). Measures relying on subjective reporting while addressing core concepts of QOL may be more vulnerable to the influence of patients' psychological states, such as depression,[204] or the level of their insight into their psychiatric problems.[205] Rating scales, on the other hand, may be subject to difficulties in separating the influence of prevalent symptoms of the illness, such as negative symptoms in the case of psychotic disorders, on ratings of QOL.

In this section we will examine recent studies in FEP that have specifically measured either subjective or objective aspects of quality of life. We have extracted this information from studies (a) that were conducted specifically to examine aspects of QOL in this patient population or (b) where a QOL measure was used as part of a treatment outcome. In addition we will also report on studies that have examined specific indexes of behavior that are likely to reflect aspects of a person's QOL. We have identified 7 studies that were specifically designed to measure QOL in patients with FEP. We also identified several publications that do not directly address the broader concept of QOL in FEP but include some indirect measures of QOL (e.g., homelessness, employment, legal problems, violence).

There are no large-scale epidemiological data available regarding the status of QOL of patients presenting with FEP in direct comparison to a matched control population. Several individual studies have, however, reported on direct or indirect measures of QOL of patients at first presentation[33, 106, 139, 150, 204, 206] and after treatment for varying lengths of time.[114, 138, 150, 207–209] None of these reports contains data on a control sample, with the exception of the Addington et al. study.[114] Two other studies[33, 208] used a more chronic sample of schizophrenia patients for comparison.

Shtasel et al. report the results of a study of psychopathology and quality of life on a sample of 37 FE and 70 chronic schizophrenia patients.[33] A factor analysis on the Quality of Life Scale items produced 3 factors: social functioning, engagement, and vocational functioning. FE patients were reported to score higher (better QOL) on QLS compared to the sample of chronic patients. Both groups of patients were performing better on the engagement factor (relationships with family, sense of purpose, empathy, etc.) of the QLS than on the other 2 factors. Browne et al.[139] report a moderately compromised QOL for a sample of 53 FE schizophrenia spectrum psychosis patients judging from the scores (mean 56.4, s.d. 20.6) on QLS,[202] with almost identical scores for male and female patients. QLS and PANSS had been administered at the time of initial presentation, presumably prior to clinical stabilization with antipsychotic therapy.

Priebe et al.[208] compared QOL between a sample of FE schizophreniform or schizophrenia patients ($n = 86$) and 2 samples of chronic patients (long stay, $n = 76$; community sample, $n = 143$) using a German version of the Lancashire Quality of Life Profile.[209–210] They report that FE patients, assessed within 2 to 4 weeks after admission to hospital, showed lower levels of satisfaction with life in general, living situation, safety, and mental health compared to the community sample of chronic patients ($p < .01$) and with safety compared to the long-stay inpatient sample ($p < .05$). After controlling for differences in levels of psychopathology, age, and gender, only the differences on the safety domain explain the overall differences in satisfaction level ($p < .01$). On objective measures of QOL FE patients reported a lower rate of unemployment (37 versus 72 and 84%, $p < .001$) compared to both chronic samples and higher rates of being victims of crime (28 versus 11%) or being accused of crime (16 versus 4%) compared to the community sample ($p < .01$).

In a larger sample of FEP ($N = 130$, 68.5% SSP) Malla et al.[206] examined domains of QOL using the self-administered Client version of the W-QoLS.[201] This instrument measures QOL on a number of domains (general satisfaction, social relations, activities of daily living, money matters, psychological well-being, symptom outlook, occupational activities, and physical health), taking into account the personal importance of the domain for the individual, and an overall index of QOL is derived from all domains. Domain scores range from −3 (worst) to +3 (best), indicating level of quality of life derived from a rather complex system of scoring, with a score of 0 regarded as neutral or indifferent. The QOL assessments were completed within 3 months following initial entry to the program after having achieved some degree of stability from acute psychotic symptoms. Patients were either neuroleptic naive or had a maximum of 30 days treatment with antipsychotics prior to entry. The results show significant variation in scores on all domains. On money matters, occupational activities, and psychological well-being the patients rated themselves consistently as having a moderately poor QOL (mean scores below 0: −0.16, −0.37, and −0.23, respectively), while on activities of daily living, social relations, symptom outlook, general satisfaction, and physical health the ratings ranged from having a reasonably good QOL to being indifferent (mean scores 2.04, 1.18, 1.26, 0.99, and 0.13, respectively). On the overall weighted quality of life index patients rated themselves as doing moderately well (mean 0.80, s.d. .85).

Female patients scored higher than males on all domains with the exception of physical health. The relatively higher self-ratings may be related to the timing of assessment (up to 3 months after admission to the program). There was no control or other patient group for comparison.

Indirect measures of QOL reported on FEP patients include legal problems and homelessness. A relatively high proportion (34%) of patients report having been involved in legal problems prior to first hospital admission.[106] These problems include mostly nonviolent episodes such as being fined, arrested, placed in a holding cell, and on probation or parole and parole officer visits, legal appointments, police contact, and/or nights in prison. In 1 study homelessness in FEP patients was reported in 15% of cases mostly before (66%) or within 24 months of hospitalization and was associated with negative symptoms but not diagnosis.[211]

Determinants of Quality of Life

Several studies specifically report on determinants of QOL,[139, 206] and several others report on factors associated with aspects of QOL as part of studies with other primary objectives.[33, 138, 150, 204, 208, 212] Browne et al.,[139] using a step-wise multiple regression analysis, report poorer QOL, as assessed with a rating scale,[202] to be related significantly to total PANSS scores ($t = -2.41$, $p < .02$) and DUP longer than 12 months ($t = -2.81$, $p < .007$). The regression model explains 19.9% of variance in QOL. The relationship between QOL and symptoms was confined to negative symptoms and the general psychopathology subscale of the PANSS. Although the findings related to negative symptoms could be influenced by some degree of overlap between negative symptoms and the QLS,[202, 213] the influence of psychopathology on quality of life has been demonstrated in other studies using self-rated measures of QOL.[213]

More recently Malla et al.[206] have examined the influence of a number of patient- and illness-related variables (e.g., age of onset, DUP, premorbid adjustment, symptom levels) separately on each domain of QOL using statistical methods not dissimilar to the Browne et al.[139] study. Their results show that different domains of patient-rated QOL are differentially related to several malleable and nonmalleable variables. For example, the "social relations" domain was related negatively to DUP ($t = -2.80$, $p < .005$), psychomotor poverty ($t = -2.40$, $p < .02$), and length of prodromal symptoms ($t = -2.50$, $p < .01$); psychological well-being, to concurrent level of depression ($t = -2.75$, $p < .007$) and premorbid adjustment in the academic domain ($t = -2.90$, $p < .005$); higher level of general satisfaction, to better social premorbid adjustment ($t = 2.16$, $p < .03$) and later age of onset ($t = 2.48$, $p < .01$); and activities of daily living, to level of premorbid adjustment in the social domain ($t = 2.05$, $p < .04$) and inversely to symptoms of psychomotor poverty ($t = -2.09$, $p < .03$). For each of the domains the variance explained by the regression models ranged from 12 to 15%. It is important to note that despite differences in the assessment of QOL, the 2 studies[139, 206] conducted in 2 different countries report on very similar samples of patients with less than 1 month of antipsychotic drug treatment and show convergence on their results, especially in the influence of potentially malleable factors such as DUP and negative symptoms on QOL.

Sim et al.[204] have used the World Health Organization Quality of Life—Brief version (WHOQOL-Bref)[200] scale as part of a study comparing QOL on FE SSP patients with and without a comorbid depressive syndrome. The WHOQOL-Bref is a 26-item self-report measure that assesses QOL on 4 domains: physical health, psychological health, social relationships, and environment. The authors report consistently lower scores for the group with ($n = 11$) compared to the group without ($n = 55$) comorbid depressive syndrome on all dimensions of QOL. Mean scores for the 2 groups, respectively, ranged from a low of 35.43 versus 48.18 for social relationships (social support, personal relationships, etc.) to a high of 44.14 versus 62.00 for environment (transport, home environment, etc.), suggesting a detrimental effect of comorbid depressive syndrome on patients' QOL. After adjusting for age, gender, education, DUP, and insight in a multiple regression analysis, the presence of unemployment ($p < .05$) and comorbid major depression were associated with poorer QOL ($p < .05$). It is difficult to interpret these results in the absence of any detailed information about the regression model. Shtasel et al., using a cluster analysis (see above), examined cluster × group (FE versus chronic) interaction and revealed primarily a main effect of cluster with only a marginal interaction effect ($p = .69$).[33] Patients in Cluster 1 (predominantly negative symptoms and thought disorder/delusions) showed the worst QOL.

Outcome on Quality of Life

We have identified several studies that report on outcome on a specific measure of quality of life. In a sample of a diagnostically heterogeneous cohort of FEP patients, McGorry et al. used the Quality of Life Scale[202] to measure QOL at 3 to 6 months following patient entry to treatment with a repeated measurement at 1 year.[150] Their results show a significant improvement in QLS scores (68.8 ± 24.7 and 82.4 ± 26.3 at 3 and 12 months). For the entire sample of 200 patients they also report a negative association between DUP and QLS scores at 1 year independent of diagnosis, gender, and age of onset, explaining 15% of variance in QLS scores. Malla et al.[207] report results on 41 FEP patients assessed within 3 months of initial entry to a comprehensive early psychosis program and 1 year later using the Client version of the W-QoLS.[201] Results show that there was a significant improvement on the overall weighted index

of quality of life ($p < .0001$) as well as individual dimensions of general satisfaction, psychological well-being, symptom outlook, social relations, money matters, and activities of daily living (range $p < .02$–$.006$). There was, however, no control group for comparison.

More recently Addington et al.,[114] using a large sample of FEP patients ($n = 177$), also have reported significant improvement (change in mean scores on QLS from 57.11 to 68.37, $p < .0005$). Women showed significantly higher scores on QLS at 1 year. Comparison among patients in remission, those not in remission, and an age- and gender-matched control ($n = 40$) showed consistently higher QLS scores for the control sample (mean 94.75) compared to both patient groups ($F = 50.21$, $p < .0005$) and the remission group to have higher scores than the nonremission group (76.5 versus 55.04). The change shown in QLS scores was, however, not controlled for initial scores on QLS. The lower QLS scores at 1 year are shown to be related to higher levels of positive and negative symptoms at initial assessment and 1 year and to poor premorbid adjustment in childhood and early and late adolescence ($F = 27.7$, $p < .0005$). This logistic analysis model explains 51% of the variance in QLS scores at 1 year and does not include DUP, gender, or level of depression or general psychopathology. Most of the variance was, however, contributed by negative symptoms (38%), although it is not clear if that was true for negative symptoms rated at initial assessment and/or concurrently. No information is provided on outcome on individual domains of QLS. The high level of influence of negative symptoms on the QLS scores reported may reflect some redundancy in variance attributed to common variance between the QLS and negative symptom measurement. Measurement of QOL with an instrument such as QLS is, therefore, likely to show greater change, as the change is partly reflective of its contributors (e.g., negative symptoms).

In contrast, Priebe et al.[208] failed to find any significant change in subjective measures of QOL at 9-month follow-up of 51 of their original sample of 86 FEP patients, although patients reported improvement in objective measures such as being accused of or having been victims of crime. Life satisfaction is likely to depend on a complex interaction among several illness- and non-illness-related factors and may take much longer than 9 months to show significant change. This is also suggested by their reports of better QOL from a comparative sample of chronic patients living in the community. Assessment of QOL being largely limited to satisfaction measures makes it difficult to interpret these results in comparison to those of other studies.

Whitty et al.[212] report data on an objective (QLS) and subjective (WHOQOL-Bref) measure of QOL for 77% ($n = 72$) of an initial sample ($n = 94$) of patients with FEP followed up 4 years after the initial assessment. The results reported suggest a marked congruence in clinicians' ratings (QLS) and self-assessment (WHO-QOL-Bref) of QOL (range of correlations $r = .53$ for the social domain to $r = .68$ for the psychological domain of the QLS) and a lack of significant influence of level of insight on the concordance between the objective and subjective measures of QOL. While the mean scores reported at 4 years following the initial assessment (82.6 and 89.4, for the schizophrenia spectrum and psychosis groups, respectively) appear to be significantly higher than that reported for the initial assessment of a smaller sample ($n = 53$, mean QLS score 56.4) from the same center,[139] no definite conclusions can be drawn about the magnitude of gain made in QOL by the patients over the 4-year period. Unfortunately the authors do not report on change over the 4-year period on either measure of QOL in the most recent study. However, this study is unique in comparing subjective and objective measures of QOL and examining the potential interference of insight in the measurement of QOL.

The above review of studies of quality of life in FEP suggests that in general there is a significant improvement in QOL in the first few years after treatment of FEP. This improvement is difficult to separate from improvement achieved in symptoms, especially when measures of QOL show a content overlap with symptoms, and it is likely that at least some dimensions of QOL are dependent on the quality and consistency of treatment. Preliminary reports from randomized controlled studies of the impact of a specialized treatment approach to FEP confirm the positive impact of specialized treatment reported from uncontrolled studies. None of the studies was designed specifically to examine the effect of interventions on QOL.

Conclusions

Considerable progress has been made in prospectively examining psychopathology from a dimensional perspective using cohorts of first-episode psychosis with a broad spectrum of diagnoses of psychotic disorders and varying periods of untreated illness; in examining trajectories of outcome over time and their relationships with psychopathological dimensions both before and after onset of psychosis; and in examining relationships among premorbid adjustment, psychopathological dimensions, and aspects of outcome. There appears to be consistency in finding a strong relation among poor premorbid adjustment, the early appearance of negative symptoms not responsive to treatment, and a trajectory of poor functional outcome and quality of life. This trajectory tends to be associated with a diagnosis of schizophrenia more often than with affective or other nonaffective psychoses. However, there also continue to be considerable variation and inconsistency in the results reported, possibly because of differences in the selection and recruitment of subjects, instruments used,

variation in definitions of outcome, and length of follow-up. Relatively small sample sizes originating from single centers and problems in integrating findings from multiple methods of investigation (e.g., epidemiological, neuroimaging, genetics) to explain variations in trajectories of outcome still remain major challenges. Another major lacuna in research in the outcome of schizophrenia spectrum psychoses is the almost total reliance on vulnerability and risk factors and the general lack of attention to resilience and protective factors.

There is a trend emerging for greater improvement in functional status and quality of life in reports from programs that are designed specifically to provide early, phase-specific, and multimodal treatment and when patients studied are representative of epidemiological samples (incidence cases) within a defined catchment area. Unfortunately these studies are based on recent cohorts and have provided data on relatively short-term outcome (1–2 years). Studies that have used more rigorously and operationally defined outcome criteria are based on relatively restricted samples of convenience or confined to those recruited from inpatient units only and, therefore, not entirely representative of incidence cases. Whether different models of treatment have differential effects on functional and QOL outcomes needs to be examined in well-controlled studies. A small number of randomized controlled trials of phase-specific comprehensive treatment for ''early psychosis'' have been completed.[214–216] The study by Nordentoft et al. is the most comprehensive, involving a large sample (n = 547).[214] Results on clinical outcome favoring the specialized service model have been reported, but no data are yet available on QOL or functional outcome. The recent randomized controlled trial by Craig et al. using a smaller sample also reports beneficial effects of a specialized service model on treatment engagement and clinical measure,[215] but no results are reported on functional outcome. The third study, by Kuipers et al., although it includes ''early intervention'' in its title, does not qualify as a treatment trial of FEP as it includes patients who had received up to 5 years of previous treatment.[216] Another issue that emerges from the plethora of studies showing a relationship between DUP and outcome is whether experimental reduction in DUP would lead to improvement in functional outcome and QOL in FEP. One study has reported a significant reduction in DUP and symptom severity for patients recruited in areas where an intensive community case-detection program was implemented compared to control communities,[166] while another study has reported considerable but statistically nonsignificant reduction in DUP following improvement in access to a specialized service.[165] The addition of a community case-identification program to the latter failed to significantly reduce DUP.[217] Similarly negative but complex results have been reported recently by Krster et al.[218] There is, to our knowledge, no report of the influence of reducing DUP on outcome on functional measures or quality of life.

Longer-term data on multiple dimensions in large cohorts of FEP patients with uniform assessment procedures, clearly defined criteria for outcome, and controlled variations in treatment models are required to answer some complex questions about trajectories of outcome and for defining patient subgroups that follow each of the outcome trajectories. Difficulties in obtaining long-term sustainable funding and limited access to large cohorts of patients, especially in single centers, may be additional obstacles to resolve. It is suggested that consortiums of FEP treatment and research programs be formed that would allow pooling of resources, expertise in methods, and uniformity in measurement. Future studies will need to pay particular attention to operational definitions of outcome and will need to examine the mediating processes, including protective factors, involved in the complex relationships that likely exist between predictors and trajectories of outcome.

Acknowledgments

We wish to acknowledge the assistance provided by Howard Fried in the preparation of this manuscript. Malla is supported by the Canadian Institutes of Health Research.

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