Improving Reliability of the Assessment of the Life Course of Schizophrenia

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Objective: Life course studies of schizophrenia that have used a 3-phase model (onset, course, and outcome) have had their use restricted owing to differences in definition and methodology. The purpose of this investigation was to describe life course data in mathematical terms and to compare the results with the findings from other life course studies.

Method: The study population was comprised of 128 of 137 people who were first admitted for schizophrenia to 1 of the 2 mental hospitals in Alberta in 1963 and followed until 1997 or death. Patient evaluations were based on retrospective and contemporaneous information collected from the patients and hospital files, treatment records, and family members. Mathematically derived ratings were formulated for course, outcome, and onset (pre-admission years). The distribution of the resulting 8 life course types was compared with profiles drawn from other such studies reported in the literature.

Results: The use of mathematical descriptions of onset, course, and outcome produced profiles that did not closely match the results of other investigations, largely owing to inconsistency across studies. Further, the present approach to outcome measurement produced results that were less favourable than those found in other studies.

Conclusions: Studies on the life course of schizophrenia could be made more comparable by specifying mathematically expressed operational definitions of onset, course, and outcome. Nonetheless, the use of the term outcome can be questioned as it implies an assessment at a specific time rather than providing a summary statement of the quality of a life.

Can J Psychiatry. 2010;55(11):729–735.

Clinical Implications

- Schizophrenia life course judgments are improved by mathematical specification of the parameters of onset, course, and outcome.
- Current results suggest a pessimistic prognosis for people hospitalized for schizophrenia.
- Investigations of onset, course, and outcome differ on many important parameters, making valid comparisons extremely difficult to realize.

Limitations

- Overall life course ratings were made by only 1 person, therefore we had no direct measure of the reliability of these ratings.
- The assessment of schizophrenia has changed somewhat since the index cases were selected in 1963.
- Although subjects were selected early, and records were consulted where possible, much of the life course information was collected retrospectively.

Key Words: *schizophrenia, first admission, reliability, onset, course, outcome, measurement*

Bleuler[1] produced an approach to the classification of the longitudinal course of schizophrenia that has been reflected in the work of Ciompi,[2,3] Harding,[4] Marengo et al,[5] and Harrison et al.[6] Although these investigators have varied their terminology and methodology, all have assigned 3 phases to the definition of the life course of schizophrenia—onset, course, and outcome. Further, each phase was ultimately characterized by 2 levels (with some variation in the terms used)—acute or gradual for onset, smooth or undulating for course, and good or poor for outcome (reduced from 4 levels in some cases). These 3, 2-level variables, when combined, form 8 life course patterns which may have use in increasing our understanding of the life course of schizophrenia.

As is often the case in applications of assessment schemes such as this, the definitions of the 3 phases differ from study to study. Further, the ratings seem to be quite subjective, and thus difficult to reproduce. Table 1 shows definitions and parameters used in the above-noted studies. Overall, diagnostic systems differed (perhaps because of the advent of new systems over time), and sample characteristics varied. Although the emphasis was on first episode cases, the definitions used were not consistent, and much information was collected retrospectively (note, however, that virtually all surveys, even those deemed to be prospective, rely, to a great extent, on recall of past events or behaviour).[7]

Ciompi's[3] definition of onset was based on the time lapse between first symptoms of mental disturbance (not necessarily psychotic in nature) and "a complete picture of a psychosis,"[p 610] with 6 months serving as the operational division point between acute and gradual onset. Bleuler[1] clearly meant onset to refer to the time period from the appearance of psychotic symptoms to the full expression of the disorder, ordinarily a few days or weeks. Bland et al[8,9] made use of a definition that referred to the time between the appearance of mental health difficulties (prodromal symptoms, with or without psychotic features) and first psychiatric hospitalization. This, in most cases, would produce a greater time span than the Ciompi or Bleuler methods. Häfner et al[10] have shown that about three-quarters of a cohort of people with schizophrenia displayed an average 5-year gap between first prodromal symptoms and the first psychotic episode. Investigations of the average gap between the first prodromal symptom and first psychotic symptom showed a range from 0.7 to 1.9 years.[11–13] Thus duration of onset will vary according to whether the period begins with first psychotic or first prodromal symptoms, and whether it ends with hospitalization or diagnosis without hospitalization.

Variability among methods aside, inaccuracy of scoring a test or observation creates a source of unreliability that is added to the unreliability of the test. Tests that produce narrative output (for example, projective tests and interviews) require subjective interpretation. Conversely, laboratory and psychometric tests can produce results in numerical form that can be easily read (scored). Thus scoring reliability could be very high in the latter case, but quite low in the former. As test unreliability and scoring unreliability are multiplicative in their effect, the consistency of scoring (for example, interrater reliability) needs to be very high—with coefficients of at least 0.90.[14]

Our study examined the consequences of applying a more objective definition of this 3-phase classification on a Canadian sample that was assessed 34 years after the first hospitalization for schizophrenia.

Methods

A detailed description of the methodology used at the inception of the study as well as the findings at 10- and 14-year follow-ups have been reported by Bland et al.[8,9,15,16]

Ethics approval was received from Alberta Hospital Edmonton and Alberta Hospital Ponoka (the 2 institutions initially involved in treating the patients) and from the University of Alberta.

The Cohort

The study cohort was drawn from the records of all people with a first lifetime admission for schizophrenia to a psychiatric hospital during 1963 in Alberta. This sample was composed of virtually all people who were hospitalized for schizophrenia as there were very few general hospital beds in the province available for psychiatric patients at that time. A meta-analysis of 320 outcome studies found no examples of a comprehensive and epidemiologically representative cohort of this nature.[17]

As patients from the 2 hospitals were reviewed for diagnosis a few years apart, changes in practice at the time produced somewhat different diagnostic criteria for the 2 sites.[9,15] Both used Schneider's[18] first rank symptoms, but the Alberta Hospital Ponoka sample was also evaluated using research diagnostic criteria,[19] while the additional instruments for the Alberta Hospital Edmonton patients consisted of a checklist for Feighner et al[20] criteria for first rank symptoms and the New Haven Schizophrenia Index.[21] Exclusion criteria were psychotic affective disorder, organic or toxic states, alcoholism, mental deficiency, and any other diagnosis that was sufficient to explain the clinical picture. The study period encompassed 35 years from 1963 through 1997 (thus 34 years of follow-up). The average duration of follow-up from first admission to the last examination was below this (30.2 years) owing to the shorter period for patients who had died prior to 1997. All patients had received medication during their initial hospitalization. Although we do not have details on the various treatments received by patients over the course of follow-up, we do have information indicating that nearly all subjects took antipsychotic medications for extended periods of time.

The original cohort totalled 137 people. Among these, 131 people were examined in follow-up studies at either 10[8,9] or 14 years,[15,16,22] with only 3 lost to the subsequent 1997

follow-up. Thus the sample was comprised of 128 people (68 males and 60 females) who were followed for the 34 years through to 1997 or until death if that occurred prior to the end of the study period. The retention of 93.5% of subjects across 34 years was achieved through contact with family members and thorough searches of clinical and provincial death records. At the study's completion, 81 subjects were living and 47 were deceased.

Procedure

Members of the cohort were assigned a rating on a 4-point scale that was designed to reflect the most significant aspect of their psychiatric functioning during each year. The anchor points of the rating scale, from most to least severe, were defined as follows:

3. Hospitalization due to mental illness.
2. Verifiable psychotic episode (diagnosed by a physician, psychiatrist, or other mental health professional), but no hospitalization.
1. Evidence of some psychiatric symptoms, but no currently assigned diagnosis and ordinarily no formal intervention, excepting some outpatient counselling. Indicators were scored below 1 if they fell within the definition of prodromal symptoms and behaviours, such as hints of positive signs (illusions, magical thinking, ideas of reference), moodiness, cognitive problems, and social withdrawal.[7]
0. Absence of psychiatric symptoms.

The ratings were made by one author who had interviewed each patient for the 10- and 14-year follow-up studies[8,15] and, for our study, had interviewed each patient who was alive at the close of the 34-year follow-up. Additional information was systematically collected from hospital files, treatment records, and interviews with family members. Ratings were based on triangulation of information from these multiple data sources, with the emphasis on the completeness of the final score[23] rather than on the confirmation of hypotheses. That is, once observed, most of the events of relevance to this assessment (for example, hospitalization, assignment of a diagnosis, or arrest) can be assumed to have occurred. The use of multiple sources will dramatically increase the likelihood that all such events will be noted and recorded. Each patient was discussed prior to the assignment of the final rating.

Intermediate rating scale values were assigned to depict variations in severity within a particular level. For example, diagnosable psychotic behaviour without hospitalization would be assigned a value ranging from 2.0 to 2.9, depending on severity. These within-category assignments were quite subjective, as the gradations were not as clear as those used for the 4 anchor points. Ratings were ordinarily assigned to reflect status for a single year, but certain years might be assigned multiple scores, depending on events. Information was recorded on each person from a point prior to the first hospitalization to the final interview or death. Although no years were missed, there were some periods where nonspecific ratings were made. For example when a report from a family member covered several years of gradual change, or when there were no significant departures from ongoing behaviour. In such cases, linear interpolation was used to produce the ratings for each period in question. Ratings for the life course of each participant were recorded graphically and are available online.[24]

Operational definitions of onset, course, and outcome are as follows.

Onset. Life course data were ordinarily assigned in 1-year segments; correspondingly, duration of onset is the number of years elapsed between the first psychiatric symptom (rating scale value = 1) and first admission to hospital (rating = 3), with 2 years serving as the dividing point between acute and chronic. However, our data allowed the operationalization of 3 additional definitions of onset, each with a different meaning. The resulting 4 views represent years from: first symptom of schizophrenia to diagnosis, first prodromal symptom (greater than zero) to diagnosis, first symptom of schizophrenia to hospital admission, and first prodromal symptom to hospital admission.

Course. The course of schizophrenia was categorized as either smooth or undulating. We defined the index of undulation to be the average distance traced by the graph (that is, the sum of the lengths of the line segments divided by the length of follow-up) divided by the largest such value for the cohort, resulting in a positive number with a maximum value of 1. The motivation for this definition rests on the observation that each change in direction necessarily increases the distance travelled. For any 2 adjacent time periods, the maximum possible distance occurs when there is a change, in either direction, between a rating of zero (no symptoms) and a rating of 3 (hospitalization). The lifetime maximum, then, occurs when there is such a reversal of direction, with each succeeding time period over the length of the follow-up. The shortest distance value is produced when there is no change over time—that is, when the line is absolutely flat.

As the creation of an index of undulation does not tell us about the optimal cut-off point between undulating and smooth, another step was required. This involved the comparison of a set of blind ratings (undulating or smooth) with the undulation index values for each case. We classified each time-series as either smooth, undulating, or indeterminate when not able to come to a clear decision. The variation of this in association with the mathematically derived undulation index was examined to determine the cut-off point.

Outcome. The outcome was represented by a score that was based on the average area under the curve for the last 3 years of available data for each person. A 3-year span was adopted to minimize any possible distortion arising from the use of 1 year for a single end-point. People with average scores below

Table 1 Comparison of methods used in selected investigations of life course

Method	Harrison et al[6] Incidence–prevalence samples	Marengo et al[5]	Ciompi[3]	Harding[4]
Diagnostic system	Mixed: converted retrospectively to ICD-10	Research diagnostic criteria	Bleuler[1]	DSM-III retrospectively
Design	Retrospective cohort	Prospective	Retrospective	Mixed
Inclusion criteria	First episode cases (incidence cases)	39% first admission	First hospitalization <65 years, lived to >65 years	First hospitalization Backward (long-stay) cases
Index age, mean years	Prevalence: 51.2 Incidence: 41.4	22.9	Males: 33.2 Females: 44.4	<25 (estimated)[27,28]
Sex, female, %	Prevalence: 40.1 Incidence: 49.4	35	68.2	50
Onset parameters	Unclear definition 1-month cut-off	Unclear (modelled on Bleuler[1] and Ciompi[3]) 6-month cutoff	First symptoms to psychosis, 6-month cut-off	Acute compared with chronic; unclear definition
Course parameters	Simple compared with episodic Determination unclear	Undulating compared with simple; assessed at 2- to 3-year intervals	Undulating compared with simple; determination unclear	Undulating compared with simple; determination unclear
Outcome parameters good or poor	Last 2 years modified Bleuler[1]: recovered or minimal, moderate, or severe	Last 5 years recovery or mild or moderately severe	Last 5 years Bleuler[1]: recovery or mild, moderately severe, severe	Global Assessment Scale >61 (recovered or mild), otherwise mild or severe
Follow-up, years	15	Up to 10	37 (average)	32
Ratings	WHO-DAS; Global Assessment of Functioning, Disability and Symptoms; Life Chart Schedule	Symptoms, hospitalizations, Rx, SADS, PSE, Katz and Lyerly Adjustment Scale	Psychiatrist records third parties	Records, third parties, clinical rating scales; modified life chart
Setting	Prevalence: 4 countries Incidence: 12 countries	Chicago, United States	Rural Switzerland	Vermont, United States

DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; PSE = Present State Examination; Rx = treatment received; SADS = Schedule for Affective Disorders and Schizophrenia; WHO-DAS = World Health Organization Disability Assessment Schedule

2.0 were classified as having a good outcome, while people with an average of 2.0 or more (that is, diagnosable mental illness) were taken to have a poor outcome.

Results

Onset

The mean age at first admission was 33.4 years (SD 10.6). As might be expected, the shortest median interval was between the first symptom of schizophrenia and its diagnosis (0.95 years), next being the time span between the first symptom of schizophrenia and admission (that is, the operational definition adopted for our analysis) at 2.0 years, followed by the gap between the first prodromal symptom and diagnosis at 4.4 years. The interval between the first prodromal symptom and hospitalization was the longest at 6.3 years. An ANOVA showed a high level of statistical significance ($F = 190.6$, $df = 3,381$, $P < 0.001$). The means, ordered as above, were 2.1, 3.4, 4.3, and 5.6 years—the differences from the median values indicating some skew. A least significance difference test (adjusted for multiple comparisons) indicated that each mean differed statistically from every other mean ($P < 0.001$).

Course

Remembering that this investigation was predicated on concerns about rater reliability, our practice of using 1 rater in the determination of the cut-off point for the statistically derived undulation index produced an interesting result. As it turned out, the undulation index was able to discriminate among the observer ratings to a considerable degree, with perfect agreement occurring at the extremes of the index. That is, all index values below 0.2 were deemed to be smooth and all values equal to or above 0.6 were rated as undulating. The discordant judgments fell within these ranges in an orderly, near-to-linear progression, peaking at an index value of just below 0.42—a suitable cut-off point for the dichotomous classification of index values as either smooth or undulating.

Table 2 Percentage distribution of cases across life course types and between each phase level for 6 investigations

Variable		Our study	Harrison et al[6] incidence	Harrison et al[6] prevalence	Marengo et al[5]	Ciompi[3]	Harding et al[28,29]
Acute smooth	good	16.4	5.3	3.5	6.8	5.3	5
	poor	3.9	9.1	2.8	13.5	8.3	3
Acute undulating	good	13.3	29.4	17.7	10.8	25.4	7
	poor	17.2	4.9	1.4	9.5	11.9	4
Gradual smooth	good	6.3	10.4	14.9	4.1	10.1	12
	poor	9.4	14.4	31.9	36.5	24.1	4
Gradual undulating	good	12.5	22.6	26.2	6.8	9.6	38
	poor	21.1	4.0	1.4	12.2	5.3	27
Onset	acute	50.8	48.7	25.4	40.5	50.9	19
	gradual	49.2	51.4	74.4	59.5	49.1	81
Course	smooth	35.9	39.2	53.1	60.8	47.8	24
	undulating	64.1	60.9	46.7	39.2	52.2	76
Outcome	good	48.4	67.7	62.3	28.4	50.4	62
	poor	51.6	32.4	37.5	71.6	49.6	38

Seven cases were deemed by the observer to be indeterminate. These cases clustered near the cut-off, ranging from 0.21 to 0.53 (mean 0.36). The index of undulation was in accord with the observer ratings in 85.9% of the cases (88.7% when half-credit was given for the indeterminate values). Overall, use of the index resulted in 35.9% being classified as smooth and 64.1% as undulating.

Outcome

According to the definition used here, 52% were assigned a poor outcome (Table 2). However, it should be noted that this is a relatively conservative measure—poor means evidence of diagnosable psychotic behaviour or admission to hospital because of a mental disorder. Had symptoms of schizophrenia been included in this category, then 80% would have been deemed to have displayed a poor outcome based on the last 3 years of follow-up.

Profiles

Onset, Course, and Outcome. The most prevalent of the 8 categories in our study proved to be the gradual onset—undulating course—poor outcome profile, which accounted for 21.1% of the cases (Table 2). The second and third most common categories, acute-undulating-poor (17.2%) and acute-smooth-good (16.4%) were more common than corresponding values found in any of the other studies (all below 12% and 7%, respectively; Table 2). It should be noted that the overall correspondence of the distribution of these 8 categories across studies was strikingly low, with Kendall's coefficient of concordance (W) standing at a near-zero level (W = 0.01, $\chi^2 = 0.36$, $df = 5$, $P = 0.99$). However, there were some meaningful similarities. The 2 Harrison et al[6] samples and the original Ciompi[3] values showed intercorrelations that were all greater than 0.65, and the Marengo et al[5] study showed moderate agreement with Ciompi and the Harrison et al prevalence results ($r = 0.59$ and 0.51, respectively). Neither the Harding[4] results nor our study profiles showed any intercorrelations above 0.35.

Discussion

The purpose of this project was to develop a methodology to aid in the description of the life course of schizophrenia, particularly regarding the 3-phase type of classification used by Bleuler,[1] Ciompi,[2,3] Harding,[4] Marengo et al,[5] Harrison et al,[6] and others. The advantage of the replacement of subjective human judgment with mathematical procedures is that the latter produces a system of scoring that is based on existing data and, apart from computer malfunctions, has perfect reliability. Conversely, a Ciompi-style method, requires subjective judgements about onset, course, and outcome that, in essence, represent an additional interpretation of the same data, with some degree of unreliability added to the assessment process.

There is no definitive explanation for the variation in the distribution of the 8 life course profiles across studies as detailed in Table 2. The variability may be due to real differences in types across cultures, populations, and time, but the methodological differences highlighted in Table 1 militate against firm conclusions. This appears to be a general issue in schizophrenia outcome research. A review of 59 studies of course

and outcome indicated that it was not possible to draw any overall conclusions because of methodological differences and weaknesses.[25] Jobe and Harrow[26] recently reviewed 10 studies that compared patients with control subjects over a period of at least a decade, and while noting that outcomes were generally poor, concluded that generalization was limited by a lack of uniformity in methods. Remedies for many of the methodological issues in schizophrenia follow-up studies have been provided by Häfner and an der Heiden,[7] and we suggest the addition of the following simple checklist based on our findings here.

Onset

The beginning point (prodromal or psychiatric symptoms) and endpoint (for example, diagnosis or hospitalization) need to be defined, as does the rationale for the distinction between acute and gradual. The North American Prodrome Longitudinal Study[27] has recently added much to our ability to understand and measure prodromal symptoms.

Undulation

The criteria used to make the distinction between smooth and undulating need to be clearly stated. This applies equally to studies using mathematical or clinical judgement approaches. Consideration should be given to the identification and isolation of indeterminate patients who fall between smooth and undulating to increase the power of the analysis.

Outcome

It is suggested that for an end-of-life outcome, that 2 or more years should be considered, as 1 year would not serve as a reliable estimate of a life. Perhaps a second category of outcome should be added that could be described as a lifetime outcome that would summarize the quality of life from onset of the disorder until death.

In situations where there is more than 1 definition of onset, course, or outcome, the various forms should be considered as variables that are eligible for study in their own right. For example, it is often feasible to create both a 6- and a 12-month cut-off for onset and to compare their effects. This would be most appropriate when it is not clear which value of the variable is optimal for the purpose of the study.

Based on the criteria adopted, just over one-half of the sample showed a poor outcome and 80% were still showing symptoms during the last 3 years of the study period. This appears to be a matter of serious concern, but comparisons with the results of other investigations of this type are restricted by the above-noted variations in methodology across studies. Further discussion on this matter is beyond the scope of our study, but will form the subject of an upcoming paper.

The use of a single interviewer–rater to assemble the dataset is acknowledged as a limitation on our ability to corroborate the consistency of measurement across time. The form of data collection (record reviews and interviews) did not lend itself to the duplication required for reliability estimation at the data collection and assimilation level. We cannot duplicate the original analysis and thus rest our position on the trade-off between the use of a skilful and continuously involved single rater, compared with the use of after-the-fact multiple raters. However, please note that this matter does not affect our demonstration that onset, course, and outcomes can be described mathematically. This could have been achieved with fabricated data as long as they had possessed parameters that approximated real-world findings.

While reliability of measurement is a crucial matter, it is not the only problem with the 3-phase approach. It is not clear what interest or use the 8 types hold. We can compare the effects of various independent variables on outcome (or other dependent variable) without invoking this model. This has added to our concern about the use of the onset-course-outcome classification of the life course of people with schizophrenia, and leads to the question of whether this is the best way to characterize a life (or a collection of lives). A particular concern is about the concept of outcome. It is unlikely that most of us would look back on our lives and consider our outcome to be represented by only the last few years of life. Most would probably be disposed to provide a summative statement that considers either all of a life, all of adult life, or, as in our study, life after the advent of a mental illness. In this context, the term outcome might be better applied to the way in which events transpire after a particular intervention and (or) after a specified period of time. For example, outcome could refer to the effects of antipsychotic medication following a clinical trial, or it could apply to a 10-year outcome posthospitalization. That is, the operational definition used to test a specific prediction about the effects of an intervention may not serve as the definition of the worth of a life.

Acknowledgements

This research was supported by grants from the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research. Neither funding body had any further role in the study design, the collection, analysis, and interpretation of the data, the preparation of the report, or in the decision to submit the paper for publication.

The authors thank Jonathan Pitcher for digitizing the life charts.

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Résumé : Améliorer la fiabilité de l'évaluation de la trajectoire à vie de la schizophrénie

Objectif : Les études de la trajectoire à vie de la schizophrénie qui ont utilisé un modèle en 3 phases (début, cours, et résultat) ont eu une utilisation restreinte en raison des différences de définition et de méthodologie. Le but de la présente recherche est de décrire les données de trajectoire de vie en termes mathématiques et de comparer les résultats avec ceux d'autres études de trajectoire de vie.

Méthode : La population de l'étude consistait dans 128 des 137 personnes qui ont d'abord été hospitalisées pour la schizophrénie dans un des 2 hôpitaux psychiatriques de l'Alberta en 1963, puis qui ont été suivies jusqu'en 1997 ou jusqu'à leur décès. Les évaluations des patients se basaient sur de l'information rétrospective et contemporaine recueillie auprès des patients et des dossiers d'hôpital, des dossiers de traitement, et des membres de la famille. Des estimations dérivées mathématiquement ont été formulées pour le cours, le résultat, et le début (années pré-hospitalisation). La distribution des 8 types de trajectoire de vie obtenus a été comparée avec des profils tirés d'autres études semblables trouvées dans la littérature.

Résultats : L'utilisation de descriptions mathématiques du début, du cours, et du résultat a produit des profils qui ne correspondaient pas de près aux résultats d'autres recherches, en raison largement de l'incohérence des études entre elles. En outre, la présente approche de la mesure du résultat a produit des résultats qui étaient moins favorables que ceux observés dans d'autres études.

Conclusions : Les études de trajectoire de vie de la schizophrénie pourraient être plus comparables en spécifiant des définitions opérationnelles, exprimées mathématiquement, du début, du cours, et du résultat. Néanmoins, l'utilisation du terme « résultat » peut être remise en question car il implique une évaluation à un moment spécifique plutôt que d'offrir un énoncé sommaire de la qualité d'une vie.