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Landmark's Model for Computerized Studies of Schizophrenia: A Review

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Abstract

Johan A. Landmark, a Canadian scientist and clinical psychiatrist of Norwegian origin, directed a large scale investigation on a sample of 120 Canadian schizophrenic patients that were rated on 87 symptoms relevant for the assessment of schizophrenia and on a multitude of sociodemographic and case history variables in order to determine if specific statistical symptom patterns would emerge as computerized clinical predictors of response to psychiatric medication, or how the symptom patterns would relate to sociodemographic variables such as gender, education, birth-order, and age. The specific symptoms and other patients' variables that significantly correlated with outcomes of psychiatric medication were entered in a statistical regression equation as mathematical predictors for future pharmacological treatments. With respect to outcomes of fluphenazine treatment at that time, the best predictor was a triad of symptoms including auditory hallucinations, passivity feelings, and disturbances of affect. This statistical approach needs to be replicated for novel antipsychotics and substances such as cannabidiol to generate statistically based predictions of which medication is the best for the individual patient with his or her particular symptom pattern, to avoid the prevalent lengthy and frustrating "trial and error" routines in daily clinical psychiatry.

The various symptoms of schizophrenia in Landmark's sample were not strongly related to any sociodemographic variables: this supports biopsychiatric concepts of schizophrenia as opposed to those based on psychosocial factors.

Keywords: *schizophrenia, antipsychotics, catatonia, gender, substance abuse, insight, suicide*

Introduction

None of the current schizophrenia treatments results in a complete recovery. The diseases within the spectrum of schizophrenia still remain poorly understood phenomena that have been mapped over the decades by various criteria none of which are fully satisfactory. The phenomenon of schizophrenia is elusively multifaceted, with some patients currently labelled as "atypical" or as with "a disease related to the spectrum of schizophrenia." In the daily clinical work in psychiatry, we need a set of predictor variables that would allow us to select the best antipsychotic for each individual patient based on his or her particular symptom patterns. The current clinical pharmacology of schizophrenia tends to proceed on a trial and error basis, rather than with a computerized mathematical model that would allow us to match the particular patient to a specific antipsychotic, to optimize treatment outcomes. To proceed in this direction, to embark on a search for statistical predictors of treatment outcomes for each particular antipsychotic, the best research approach is to prepare an exhaustive list of variables relevant in schizophrenia research to serve as potential predictors, including recently postulated variables of biological, biochemical, or genetic nature as well as sociodemographic variables and those from the patients' medical history. This would create a basis for the statistical search for possible correlational leads.

To proceed in this direction, Johan Landmark created a manual [1] with rating schedules for 87 variables relevant for diagnosing or research on schizophrenia as well as over 70 sociodemographic variables and those from the patient's medical history. His

manual should be updated to include variables that emerged as important from more recent studies of schizophrenia. The data collected with his clinical tool, when computerised, are a potential goldmine for exploratory studies that could lead to a more profound understanding of schizophrenic illness and allow us to more successfully predict outcomes of particular pharmacological treatments. As will be shown in the following pages, using an extensive list of all symptoms relevant for research on schizophrenia on a large sample of patients also allows us to conduct numerous scientific studies on the same data set, studies such as on gender differences in symptom profiles, or on symptom differences related to educational level or to age of onset, or even to variables such as birth order, or to investigate the correlates of special symptoms such as those of catatonia: this is a great advantage of the computerized Landmark's approach to schizophrenia studies.

Materials and Method

Landmark's Sample of Patients

Landmark's sample consisted of 120 patients (mean age 38.2 years, SD=9.8, range 20 to 65; 73 women, 47 men) in a government operated psychiatric hospital in Canada, see details in Cernovsky et al. [2], Landmark et al. [3]. All had been clinically diagnosed at least once as schizophrenics in hospital settings. All except 6.7% met the DSM-III criteria for schizophrenia. Excluded were patients with organic brain syndromes, those with obvious symptoms of psychoses other than schizophrenia, those with sensori-motor handicaps, and those with subnormal intelligence. They were hospitalized for schizophrenia on the average 4.5 times (SD=2.3) before. About one half (48%) had suffered from their illness for more than 2 years. At the time of Landmark's collection of data in 1970s and early 1980s, all these patients were stabilized on fluphenazine decanoate or enanthate.

The number of patients in the correlational studies reported below was at times smaller than 120 because the information for certain variables of interest (e.g., educational level) was not available for some patients, however, the sample size was never below 100.

Assessment Instrument

The patients were assessed individually by means of the manuscript version of Landmark's manual [1]. The manual includes a checklist of 88 symptoms relevant for research on schizophrenia, see full list also in Cernovsky and Landmark [4], however, the ratings for Item 51 ("increase by sodium amythal I.V.") were available too rarely in Landmark's sample of patients. Thus we investigated only the 87 symptoms.

Landmark's manual also allows the clinician to rate each patient on 70 sociodemographic variables and variables based on the patient's medical history, see Cernovsky, Landmark, and Leslie [2]. The computerized personal medical history data thus included the number of past psychiatric hospitalizations, number of times diagnosed as schizophrenic in hospital settings, age at first hospitalization, total number of months spent as inpatient in psychiatric hospitals, and also ratings of premorbid adjustment. The sociodemographic variables included the present occupation and present social position, educational level, gender, number of siblings, and birth order (rank position within siblings), see Landmark's manual [1].

Information for coding all variables was based on interviews with patients and their relatives as well as on casebook data. Each symptom was rated as present when it was noticed at least once in the past or during the research interviews. In cases of doubt (e.g., when evaluating ambiguous indirect information from a relative), the symptom was conservatively coded as absent. The scoring of symptoms of schizophrenia was dichotomous (present=1, absent=0).

Results And Discussion

Relationship of Schizophrenic Symptoms to Sociodemographic Variables

Using the computerized list of 87 symptoms as in Landmark's manual [1] made it less likely that relationships of some relevant aspect of schizophrenia as indicated by a particular symptom profile to other variables would be missed.

Education

Education has a powerful psychosocial impact on personality characteristics by shaping the values, behaviours, cultural participation, and lifestyle. We examined whether individual schizophrenic symptoms are different in patients with higher education than in those at lowest educational levels, see Cernovsky, Landmark, and Helmes [5]. All patients in this study (N=108, 41 men, 67 women) met DSM-III diagnostic criteria for schizophrenia and their educational level

was known. In this group, 6.7% had a professional degree, 2.5% an undergraduate degree, and 6.7% had been through college, 25.8% finished highschool, 51.7% junior highschool, and the remaining 6.6% had at least grade 8 education. The significance level was set to p = .01, 2-tailed, to minimize chance findings. The ratings of 87 symptoms relevant for diagnosing schizophrenia were unrelated to the educational level (point biserial coefficients, p>.01). The exceptions to this trend were ratings of apathy, insight, and of premorbid adjustment: patients with higher education were less frequently labelled as apathetic (r=.28), or as lacking insight (r=.26), and their premorbid adjustment was better (r=.25). The lack of stronger correlations suggests that schizophrenic symptoms might be largely uncorrelated with skills acquired in the process of higher education.

Gender

Reviews of gender differences in schizophrenia report an earlier onset in males than in females (see Eaton [6] and Torrey [7]), a more chronic, unremitting course in males and parallel differences in social and psychosexual adjustment, work stability, and frequency of antisocial behaviours (see Flor-Henry [8], Wattie and Kedward [9]). These differences could partly reflect cultural sex role expectations or premorbid differences in social competence occasionally reported in schizophrenia research (Zigler and Levine [10]). Cernovsky, Landmark, and O'Reilly [11] statistically cross-tabulated the data of symptom presence versus absence by gender and calculated phi coefficients between gender and the 87 symptoms. All significant correlations were only weak (phi coefficients < .30) and suggested that males had a more gradual illness onset, more often lacked in initiative and motivation, were rated as showing more deterioration over time, and less likely to spontaneously return to premorbid level than were the female patients. Premorbid adjustment was rated as slightly better in women than in men.

The age of onset was only slightly lower in men (mean age 24.9, SD=7.5) than women (mean 26.1, SD=7.0): the difference was not significant in the t-test (t=.86, p=.196, 1-tailed).

All these relationships involving gender were only weak and therefore are not clinically useful for predicting outcomes of schizophrenia with individual patients.

Birth Order, Family Size, and Schizophrenic Symptoms

Our study [12] was carried out on 107 schizophrenic patients (42 men, 65 women) who met the DSM-III criteria for schizophrenia and for whom their birth order position was known. Forty patients (37.4%) were first-born, 29 second (27.1%), 18 third (16.8%), 10 fourth (9.3%), and 4 fifth (3.7%), 2 sixth (1.9%), 3 seventh (2.8%), and one patient was the ninth-born child. The average number of siblings was 3.7 (SD = 2.2). Only one patient had no siblings. The criterion of significance was set to .01 (2-tailed). Birth order was not significantly related to any of the 87 symptoms relevant for diagnosing schizophrenia, see Cernovsky, O'Reilly, and Landmark [12].

The number of siblings was not significantly correlated with any of the 87 symptoms, except for the following three: ideas of reference (r=-.28, p=.004), difficulties in thinking (r=.28, p=.004), and treatment outcomes with fluphenazine (r=32, p=.001). The first of these three variables referred to the patient's paranoid beliefs: the patients with such beliefs were more often from smaller families. The second variable involved difficulties concentrating and with excessively slow flow of thoughts: patients from larger families reported such problems more frequently. The third variable measured treatment outcome with fluphenazine: patients from larger families had better outcomes. While significant, all these relationships were only weak and of little relevance for clinical predictions.

Relationships of Schizophrenic Symptoms to the Patients Psychiatric History, Behavioural Issues, and to Selected Other Psychiatric Symptoms/Syndromes

Age of Onset

According to Bleuler's [13] data, about 83 to 85% of patients developed schizophrenia before or by the age of 40. Later onset may be associated with more paranoid symptoms. Angst et al. [14] reported that 35% of cases of paranoid schizophrenia began after the age of 40 and 13% after the age of 50. Less severe deteriorations was usually reported for patients with later onset (Hamilton [15]). A possible major confounding factor in such studies is the duration of illness, i.e., chronicity: this bias can be statistically controlled for by partial correlation coefficients. These partial correlation procedures were carried out in our

study [16] on 112 patients (average age 38.1 years, SD=9.8, range from 20 to 65 years; 42 men, 70 women). All met DSM-III criteria for schizophrenia. Their age at the time of first hospitalization for schizophrenia ranged from 16 to 59 years (average at 25.7 years, SD=7.2). We used the age at first hospitalization as a conservative objective estimate for the actual age of onset.

None of the correlation coefficients between age of onset and the 87 symptoms was significant at p=.01, 2-tailed. This was true both for correlations corrected for chronicity and for the uncorrected ones [16].

Non-Compliance

Noncompliance, or the failure of patients to regularly take medication as prescribed by the physician, is a particularly serious problem in the patients with schizophrenia. At the time of Landmark's research, almost all patients not treated with any form of antipsychotic medication relapsed within three years [17]. Our team [18] evaluated correlates of noncompliance followed by rehospitalizations within one year on the sample of 104 patients (mean age 38.2 years, SD=9.9; 41 men, 63 women) for whom compliance data were available: all met the DSM-III criteria for schizophrenia.

Socio-demographic and clinical data as per Landmark's manual [1] were also included in the analysis, e.g., also the occupational status, coded as in Hollingshead and Redlich [19]. In our analyses of data, episodes of noncompliance followed by rehospitalizations within one year were found in 31.7% of our patients (i.e., 33 of 104). Noncompliance was not significantly related (Pearson rs, with p set to .01, 1-tailed) to any of the sociodemographic variables except to less adequate premorbid adjustment (r=.33, p=.001). Only 3 schizophrenic symptoms were correlated with noncompliance: signs of autism (r=.32, p=.001), widespread delusions (r=.25, p=.01), and persistent persecutory delusions (r=.28, p=.004), defined as in Landmark [1].

We included all four potential predictor variables (autism, premorbid adjustment, widespread delusions, and persistent persecutory delusions) in a multivariate analysis. The multiple correlation coefficient (R) was .47, p<.001. The adjusted R^2 suggested that these four variables accounted for only about 18% of variance in our noncompliance data.

Unlawful Conduct

The relationship of schizophrenia to crime is a controversial topic. Depending on the sampling method, very different conclusions were reached in the past. Violent schizophrenics tend to be transferred to specialized forensic or correctional settings. Glancy and Regehr [20] indicated that schizophrenics are overrepresented in correctional settings and are frequently involved in violence perpetrated in emergency rooms, pre-admission settings, and after admission to hospital. Patients remaining in general psychiatric hospitals may often have crime rates lower than the general population [21]. Martell and Dietz [22] investigated 20 offenders who pushed or attempted to push their victims onto the subway tracks in New York City and found that most of these offenders were diagnosed with schizophrenia. Although 14 of these persons suffered from persecutory delusions, these delusions were seen as the primary motive for their crime in only three of these offenders.

Some empirical studies suggested that schizophrenia is a risk-reducing and protective factor with respect to crime [23]. Porporino and Motiuk [24] found that mentally disordered offenders were at reduced risk to commit further serious crimes while posing a relatively greater risk to commit minor "nuisance" offenses. Ogloff [25] concluded that schizophrenia may actually be inversely related to violence. The magnitude of risk contributed by factors such as younger age, male gender, and socioeconomic status is usually more substantial than that contributed by mental illness [26].

Our study, see Cernovsky, Landmark, Oyewumi, Litman [27], was based on 111 patients (average age 38.3 years, SD=9.7; 41 men, 70 women) who met DSM-III criteria for schizophrenia. The violent and non-violent crimes were recorded separately as well as those linked directly to excessive consume of alcohol or illicit drugs, or those clinically seen as directly linked to the patient's psychosis, and those free of a context of substance abuse or psychosis.

At least some unlawful conduct during the adult years was reported in 33.3% of our patients. Men were disproportionately often represented among the perpetrators (63.4% of men versus 15.7% women; phi=.49, p<.001).

The majority of these perpetrators (86.5%) were involved in nonviolent crimes only and 25% of these nonviolent perpetrators were under the influence of alcohol or illicit drugs while committing the crime and another 25% were acutely mentally ill during their act. Only 5 patients were involved in violent crimes. When we combined all crime categories into one dichotomous variable (unlawful conduct absent = 0 versus present = 1), this variable was associated significantly ($p<.01$, 2-tailed) with a history of past alcohol abuse (phi=.47, $p<.001$) and drug abuse (phi=.43, $p<.001$) as well as with present use of alcohol (phi=.28, p=.003). The law-abiding patients had more satisfactory ratings of their premorbid competence ($r=.34$, $p<.001$) and were less frequently changing their address in the last 5 years ($r=.29$, p=.003).

Only 3 symptoms of schizophrenia were significantly correlated with unlawful conduct: unreliable information (phi=.34, $p<.001$), poor rapport (phi=.32, p=.001), and deterioration over time (phi=.26, p=.006). Patients with a history of unlawful conduct more often provided unreliable information, showed a poor rapport, and also a progressive deterioration. Except for substance abuse, all underlying correlations are only weak. The substance abuse seems to be the only salient potential predictor of delinquency in chronic patients with schizophrenia.

Attempted Suicide

It is estimated that about 10% of schizophrenics eventually die from suicide, see Miles [28]. Our study [29] was based on 118 patients in Landmark's sample who had adequate data with respect to suicide attempts or suicidal ideation. Of these 118 patients, 23% had a known history of serious suicide attempts and 12% of repeated attempts. Our correlational analysis indicated that neither the symptoms of schizophrenia nor sociodemographic or case history data were significantly correlated with suicide attempts. The only exceptions were variables related mainly to chronicity: patients with suicidal history had more frequent past psychiatric admissions (Kendall's tau=.42), were more frequently diagnosed as schizophrenic in the past (Kendall's tau=.35), their work function was rated as more poor (Kendall's tau=.35), and they more frequently changed addresses (Kendall's tau=.34).

Substance Abuse

Our analyses [30] were carried out on a sample of 110 patients, all meeting DSM-III criteria for schizophrenia, for whom information on substance abuse was available. Substance abuse was a problem in 45.5% of these patients and was significantly more frequent in males than in females (69.1% versus 30.9%). Surprisingly, those engaging in substance abuse presently or in the past did not differ significantly from those free of substance abuse with respect to the length or number of psychiatric hospitalizations, after we controlled our data for age by means of partial correlation coefficients. Further analyses examined correlations of substance abuse to symptoms of schizophrenia. Delusions were more frequently expressed by those presently abusing alcohol (53.3% versus 17.9%, phi=.29, p=.002).

Those abusing drugs were more frequently rated as showing a phasic course of illness (27.3% versus 4.0%, phi=.29, p=.003). Those abusing drugs were also more likely to exhibit symptoms of illnesses other than schizophrenia, in addition to schizophrenic symptomatology, than those not abusing drugs (27.3% versus 4.0%, phi=.29, p=.003). All these correlations were weak.

Catatonic Symptoms

Catatonia is a striking phenomenon, now seen rarely, and mostly encountered in cases of untreated or treatment resistant schizophrenia. At the time of Landmark's collection of data, catatonia was described as motor anomalies, in the form of stupor or rigidity with protracted inappropriate posturing, sometimes combined with muteness or near muteness, stereotypies, echopraxia, or automatic obedience, or at the other extreme, as psychomotor agitation that may be combined with incoherent verbal productivity, potentially violent destructive behaviour, and a medical risk of collapse from complete physical exhaustion [31]. Catatonic syndromes also occur in various mental disorders other than schizophrenia. Fink and Taylor [32] argued that catatonia should be considered as a separate diagnostic category, distinct from schizophrenia. A noteworthy extensive treatise on catatonia was prepared by Caroff, Mann, Francis, and Fricchione [33].

Our analyses on catatonia [34] were carried out on a sample 112 patients who fulfilled the DSM-III criteria for schizophrenia (mean age 38.1 years, SD=9.8;

70 women and 42 men). Catatonic symptoms were scored as present if any of the following was observed: catatonic stupor, catatonic excitement, automatism, flexible or rigid catalepsy, stereotypies, echopraxia, and negativism. As reported elsewhere, see Helmes, Landmark, and Kazarian [35], the inter-rater reliability for the raters' ratings of these catatonic symptoms on our patients, using Landmark's manual]1], was satisfactory (kappa coefficients > .55).

Forty-five (40.2%) of our patients showed catatonic symptoms, either presently or in the past. The criterion of significance was set to p=.01 (1-tailed). Only weak phi correlation coefficients were found and most of these correlates could be interpreted as aspects of catatonia: bizarre mannerisms (phi=.28, p=.002), peculiar or altered behaviour (phi=.23, p=.008), increase or decrease of motor activity (phi=.26, p=.003), and elated or unstable mood (phi=.24, p=.006). This suggests that catatonic symptoms occur to a large extent independently of the specific patterns of schizophrenic symptoms.

Correlates of Insight

Our analyses [36] were carried out on 111 schizophrenic patients diagnosed in accordance with DSM-III. Of the 111 patients, 108 (97.3%) showed poor insight into their illness at some time in the past and 65 (58.6%) at the time of assessment. Those presently showing poor insight were significantly (Pearson rs, p< .01, 2-tailed) more frequently rated as currently displaying poor judgement also in other matters (r =.50), as showing social withdrawal (r=.42), poor rapport (r=.33), as being preoccupied with their delusions or hallucinations (r=.31), and as being unreliable informants (r=.41). They usually had lower education (r=.33), their income in the last taxation year was lower (r = .47), and their work functioning was less adequate (r = .30) [36].

Hysterical Symptoms

Hysterical symptoms are mainly only of historical interest in contemporary psychiatry, see Merskey [37]. In Landmark's data, 37.0% of our 112 patients who met the DSM-III criteria for schizophrenia showed hysterical symptoms either in the past or at the time of the interview [38]. These symptoms were not significantly correlated (phi correlation coefficients, p>.01) with any of the schizophrenic symptoms from Landmark's manual [1], see details in Cernovsky and Landmark [38].

Outcome of Fluphenazine Therapy

Fluphenazine was still used in Canadian hospitals at the time when Landmark's data were collected. Our statistical analyses [39] indicated that the 3 following symptoms, i.e., auditory hallucinations, disturbances of affect, and passivity feelings (referred to at times as Landmark's triad), were found to be more highly correlated with successful outcomes of fluphenazine treatment than any other of 13 past traditional diagnostic systems (including DSM-III at that time), and also more than any other symptoms and any socioeconomic or case history variables listed in Landmark's manual [1].

It is possible that pharmacotherapeutic outcomes even with some newer antipsychotic medications could be optimized if using a similar statistical approach of matching the best outcomes with specific symptom patterns, using similar (but updated) extensive computerized lists of all symptoms relevant for research on schizophrenia.

Heuristically, Landmark's computerized approach is valuable as a general model for isolating potential predictors of treatment success of pharmacotherapy in general.

Further research is much needed to replicate the broad based Landmark's methodology with newer medications to isolate symptom clusters predictive of positive outcomes for each of the newer antipsychotic agents. These studies should also include cannabidiol (CBD) as it was recently shown to control schizophrenic symptoms equally well as amisulpride and with less side-effects, see Leweke et al. [40].

Conclusions

Our studies on the data set collected by Johan Landmark on his sample of 120 Canadian schizophrenic patients, using his comprehensive list of symptoms of schizophrenia as well as his list of sociodemographic and case history variables [1], indicated that schizophrenic symptoms are, with only minor and week exceptions, unrelated to psychosocial or demographic factors such as the patients' educational level, gender, or the patient's birth order, or the family size as operationalized by number of siblings. This lack of strong relationships is another piece of circumstantial but valuable evidence that further supports biopsychiatric etiological concepts of schizophrenia.

The main contribution of Landmark's schizophrenia research lies in statistically investigating an unusually wide spectrum of potential sociodemographic and personal history correlates of symptoms of schizophrenia as well as the correlations to treatment outcomes, suicide attempts, noncomplicance with medication, and violent behaviour.

Current pharmacological research is usually restricted by its prevailing model of comparing a given medication to placebo or to a rival drug, unlike in Landmark's approach which attempted to predict the outcomes via determining which particular profiles of schizophrenic symptoms are best correlated with pharmacotherapeutic outcomes.

Further research on psychoses might greatly benefit from expanding Landmark's approach to also include any symptoms relevant for studies of mood disorders. Hopefully, this more inclusive and encompassing approach would eventually allow for more precise pharmacotherapy, with more adequate predictions of which medication would most benefit a given patient with his or her particular symptom pattern.

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