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Longitudinal progression of negative symptoms in schizophrenia: A new look at an old problem

Mary E. Kelley [a,*], Gretchen L. Haas [b,c], Daniel P. van Kammen [d]

[a] Department of Biostatistics, Rollins School of Public Health, Emory University, Atlanta, GA, United States
[b] VISN 4 Mental Illness Research, Education and Clinical Center (MIRECC), VA Pittsburgh Healthcare System, Pittsburgh, PA, United States
[c] University of Pittsburgh School of Medicine, Pittsburgh, PA, United States
[d] CHDI, Inc., New York, New York, United States

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Abstract

Objective: Longitudinal analysis is crucial in determining the ability of new interventions to successfully reduce negative symptoms in schizophrenia. However, there are still conflicting reports as to whether there are significant treatment effects on these symptoms and the extent of these effects. We examine the possible effects of analysis method on these questions.
Methods: We use generalized linear mixed models (GLMM) to assess the change in specific negative symptom items following treatment changes in two separate cohorts of schizophrenia patients, one chronic and one first episode.
Results: Both data sets indicate that examining the change in prevalence of moderate to severe symptoms provides a useful estimate of the effect size associated with changes in treatment that often differs from that given using analysis of means.
Conclusions: The use of categorical longitudinal methods may be critical to determining the responsiveness of negative symptoms to treatment as well as determining the stability of these symptoms over time.

Keywords: Negative symptoms; Longitudinal data; Ordinal data; Symptomatology

1. Introduction

Negative symptoms are a primary focus of treatment and rehabilitation in schizophrenia patients (Stahl and Buckley, 2007), and longitudinal studies of these symptoms are paramount to establishing treatment efficacy. The early studies of schizophrenia often considered negative symptoms to be more stable and enduring than psychotic symptoms (Johnstone et al., 1987; McGlashan and Fenton, 1992; Pfohl and Winokur, 1983; Pogue-Geile and Harrow, 1985; Venables and Wing, 1962), as well as refractory to pharmacologic intervention. Crow (1980) further proposed to divide schizophrenia into two subtypes, each characterized by the predominance of one type of symptoms over the other. Type 1 patients exhibited mainly positive symptoms, while Type 2 patients showed mainly negative symptoms. Others proposed a third, disorganized subtype (Andreasen and Olsen, 1982; Bilder et al., 1985; Liddle, 1987).

* Corresponding author. RSPH, Rm 352, 1518 Clifton Rd NE, Atlanta GA 30322, United States. Tel.: +1 404 712 0804; fax: +1 404 727 1370.
E-mail address: mekelle@emory.edu (M.E. Kelley).

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Later observations, however, revealed significant changes in negative symptoms over time (Kay, 1990; McGlashan and Fenton, 1993; Mueser et al., 1991) that were related to changes in psychosis (Addington and Addington, 1991; Miller et al., 1994; van Kammen et al., 1990) and medication treatment (Goldberg, 1985; Rosen et al., 1984; Tandon et al., 1990, 1993). In addition, the subtype classifications were also shown to fluctuate over time (Andreasen et al., 1990; Arndt et al., 1995; Eaton et al., 1995; Fenton and McGlashan, 1992; Marneros et al., 1992). These conflicting observations led to the idea that the persistence, rather than the presence, of negative symptoms may more reliably identify a clinically relevant subgroup of patients. This then led to classifications based on longitudinal presentation, such as the deficit syndrome (Carpenter et al., 1988) and a revisiting of the Kraepelinian subtype (Keefe et al., 1987, 1996). The deficit syndrome has been a useful construct for identifying a group of patients with a more severe form of the illness that may require more aggressive or entirely new modalities of treatment (Buchanan and Carpenter, 2001; Carpenter et al., 1999).

More recent evaluation of the benefits of pharmacological treatment on negative symptoms has demonstrated either limited effects or inconsistent results (Alphs, 2006; Buchanan et al., 2007; Buckley and Stahl, 2007; Erhart et al., 2006; Lieberman et al., 2003). While much of this is due to design concerns such as measurement and control of possible secondary effects, a primary concern is clinical relevance or effect size (Alphs, 2006; Buckley and Stahl, 2007; Kirkpatrick et al., 2006). For the quantification of longitudinal changes, most recent assessments have used linear mixed models that provide substantial improvement over standard linear models such as ANOVA and MANOVA (Gibbons et al., 1993; Gueorguieva and Krystal, 2004). This is partly due to the fact that mixed models provide more flexibility by allowing the inclusion of subjects that have some missing data without introducing the bias found with approaches such as last observation carried forward (LOCF) (Elliott and Hawthorne, 2005). More importantly, however, these models explicitly incorporate terms that reflect subject level heterogeneity; i.e., they can take into account the fact that subjects differ in both their severity of illness at baseline as well as their rate of response. These models are well suited to the analysis of summary measures such as total scores and have been used for the assessment of treatment effects on negative symptoms (Buchanan et al., 2007; Lieberman et al., 2003).

However, it would also be of interest to assess the effects of treatments on the individual symptoms, such as affective flattening, that are measured on an ordinal scale. Unfortunately these data do not meet the assumptions of these linear methods that require continuous data. Recently, the development of generalized linear mixed models (GLMM) has provided analysts with analogues to these linear mixed models for use with categorical (e.g. ordinal and binary) data (Rabe-Hesketh et al., 2002). However, most assessments of longitudinal change in negative symptoms either have not analyzed individual symptoms or have not employed these methods because they were not readily available until more recently. However, it may be important to make use of these methods because using linear methods on categorical data results in biased estimates (Lipsitz, 1992), which may subsequently alter the significance of effects. More importantly, continuous data methods are especially biased when many subjects have no evidence of a symptom (Hastie et al., 1989). In that case, the variance is even further reduced and we are essentially measuring prevalence and not average severity across subjects. For these reasons, the use of categorical methods for the analysis of longitudinal symptom data may provide both an opportunity to further explore treatment effects as well as give more meaningful estimates of the mutability of symptoms than would a continuous analytic approach.

For the current study, the aim was to propose the analysis of prevalence as an alternative measure to quantify and visualize the patterns of change in negative symptoms over time. Two different experimental paradigms were used to evaluate the effects of treatment changes on negative symptoms: 1) following drug discontinuation in chronic schizophrenia inpatients and 2) after initiation of treatment in a group of first episode schizophrenia patients. As an example of the possible effects of analysis choice on interpretation, we produce and compare the significance of the changes over time (slopes) with those of similar linear models run on the same data.

2. Methods

2.1. Subjects

2.1.1. Chronic schizophrenia

This cohort consisted of 100 male veterans admitted to the Schizophrenia Research and Treatment Unit (SRTU) at the VA Healthcare System in Pittsburgh, Pennsylvania. Admission to the study followed completion of oral and written informed consent, in compliance with the policies of the Highland Drive VA Medical Center's Institutional Review Board (IRB). All subjects