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Heterogeneous depression trajectories in multiple sclerosis patients ☆

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ABSTRACT

Background: Trajectories of depression over time may be heterogeneous in Multiple Sclerosis (MS) patients. Describing these trajectories will help clinicians understand better the progression of depression in MS patients to aid in patient care decisions.
Methods: Latent class growth analysis (LCGA) was applied to 3507 MS patients using an electronic health records (EHR) data base to identify subgroups of MS patients based on self-reported depression screening (PHQ-9). Latent trajectory classes were used for group comparisons based on baseline clinical characteristics.
Results: Three subgroups were found characterized by high (10.0% [of participants]), wavering above and below moderate (26.2%) and low and variable (63.8%) depression level trajectories. The subpopulation trajectories, respectively, were also characterized by high, moderate and low MS disability at baseline. In contrast, the overall average trajectory was slightly declining and below the moderate depression threshold.
Conclusion: The LCGA approach described in this paper and applied to MS patients provides a template for improved use of an EHR data base for understanding heterogeneous depression screening trajectories. Clinicians may use such information to more closely monitor patients that are expected to maintain high or unstable depression levels.

1. Introduction

Depression is the most frequent psychiatric diagnosis in Multiple Sclerosis (MS) patients, with lifetime risk estimated at ~50% (Panel, 2005; Siegert and Abernethy, 2005). Patients with MS show increased severity of depressive symptoms compared to patients with other chronic neurological conditions (Wallin et al., 2006).

Depression in MS is also extremely complex. Many of the symptoms of MS such as fatigue, cognitive impairment, and physical impairment mimic the symptoms of depression (Gunzler et al., 2015; Gunzler and Morris, 2015). In particular, somatic confounders from symptoms of MS may have a large effect on measures of depression in MS patients (Ferrando et al., 2007; Gunzler et al., 2015; Gunzler and Morris, 2015; Skokou et al., 2012). In addition, some of the disease-modifying therapies for MS, such as beta interferon therapies, list depression as a side effect (Feinstein, 2000). A clinician caring for a patient suffering symptoms of both depression and MS, may need to evaluate in particular how depression evolves in MS patients, given these complexities.

Major depression may be a heterogeneous condition in which MS patients exhibit different long term trajectories based in part on the severity of their particular MS symptoms and depressive symptoms (dedeRoon-Cassini et al., 2010; Goldberg, 2011; Uher et al., 2010) along with the complex interaction between the co-occurring conditions. Describing the different potential depression trajectories of subgroups of MS patients will help clinicians better understand the progression of depression in MS patients to aid in patient care decisions.

Latent Class Growth Analysis (LCGA) allows us to identify meaningful unobserved subpopulations within a larger population to examine the subgroup growth trajectories over time. Thus, we can use LCGA to describe distinct subgroups of MS patients based on longitudinal mental health outcome trajectories.

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Some prior studies over a similar time range as covered in our Electronic Health Records (EHR) database under study (approximately four years) did not observe substantial average depression trajectory changes in MS patients using the Center for Epidemiological Studies Depression Scale (CES-D) (Beal et al., 2007; Koch et al., 2015; Radloff, 1977). Thus, these studies provide further background for the importance of exploring subgroup analyses for possibly describing subgroups of MS patients that do show depression trajectory changes. Similar LCGA approaches have been used to identify different latent classes of patients using mental health scales representing quality of life, depression severity and stress (dedeRoon-Cassini et al., 2010; Klotsche et al., 2011; Uher et al., 2010).

Our approach will use an EHR database to provide clinicians with an understanding of different depression trajectories of MS patients. We will also examine the association between these subpopulation trajectories and anti-depressant treatment, MS disease modifying therapy, MS symptoms and demographic information at baseline. Further, we will examine for potential divergence between affective and somatic depressive symptom trajectory subgroup patient classifications. Clinicians may then begin to use these methods for monitoring patients that are more likely to cluster into subgroups marked by high or volatile depression trajectories.

2. Material and methods

2.1. Study design and KP data base

Cleveland Clinic's Knowledge Program (KP) (Katzan et al., 2011) links patient-reported PHQ-9 data to its EPIC (Epic Systems Corporation, Verona, WI, USA) EHR, yielding powerful opportunities to study and improve patient care and clinical research. The Mellen Center (Mellen Center for Multiple Sclerosis Treatment and Research, 2013) for Multiple Sclerosis manages more than 20,000 visits and 1000 new patients every year for MS treatment. The KP tracks illness severity and treatment efficacy over time across the Mellen Center population.

We use a retrospective cohort study design. The inclusion criteria for our sample includes patients making at least one visit to the Mellen Center with measurements of PHQ-9 score and a timed 25-foot walk available. Data are available for 3507 MS patients from 2008 to 2011 that meet our inclusion criteria at baseline. This study has received approval from the IRB at The MetroHealth System, Cleveland, Ohio.

The sample mirrors the United States' MS population in that MS is typically diagnosed in patients in their early 30s, Caucasians are of highest risk and females are twice as likely as males to develop MS (Gunzler et al., 2015; Panel, 2005). In our baseline sample, 73% were female, 83% were white, and the average age was 46 (SD=12). These patients had their first MS symptom an average of 10 (SD=9) years ago with 81% relapsing (combination of relapsing-remitting and other types of relapsing patients) and 16% progressive (both primary and secondary progressive patients) with the remaining patients falling into other categories, or under evaluation for a potential MS diagnosis. We excluded patients who are not relapsing or progressive (N=70) from our analyses based on MS type, due to our uncertainty about their diagnosis.

If a follow-up visit was less than one month later, we either did not consider it in the longitudinal data set or merged any new recordings to fill in missing data for the prior visit. The reason we collapsed visits less than one month apart was that these might not have been new visits, but just additional information added in the EHR database about the patient. Further, these entries may have been partial visits for the purpose of clinical surveillance of a more acute problem. Patients were seen an average of 3.9 times (SD=1.5) during the KP to date. Most (77%) of the patients returned for a second visit in the available data window, and just over four-fifths (81%) of those patients made a third visit. Similar drop-off patterns emerged through the first eight visits, and 402 patients have at least seven follow-up visits. Visits to the Mellen Center after the first visit occur irregularly, with about half of the patients seen again within 6 months.

More severely disabled MS patients might be inclined to visit the Mellen Center more frequently, thus leading to the possibility of nonignorable missing data patterns. However, our inclusion criteria of a recorded timed 25-foot walk eliminated anyone who was completely immobile from this dataset (also randomly eliminated some patients without a timed walk recorded in the EHR system). Further, we also examined if number of visits per patient was correlated with symptom severity (baseline total PHQ-9 score, MS-related fatigue, MS-related cognitive impairment, timed walk and peg test) and the Pearson correlation was less than 0.10 in all five cases.

2.2. Measures assessed

The PHQ-9 (Blacker, 2005; Kroenke et al., 2001) screens for and monitors depression. A self-reported depression screening tool, the PHQ-9 is meant to be used in connection with expert clinical judgment and/or further rating tools (Blacker, 2005) and not as an individual tool to diagnose depression. Patients specify frequency in the past 2 weeks (0=not at all to 3=every day) of nine symptoms, yielding a total score (range: 0–27). Scores on this self-reported instrument are often used to guide treatment decisions (Kroenke et al., 2001). In particular, a PHQ-9 $\geq$ 10 has been previously established as a screening cutoff for depressive disorder (Ferrando et al., 2007; Kroenke et al., 2001). The PHQ-9 has been validated using multiple modes for administration, clinical populations, and diverse race/ethnicity groups (Pinto-Meza et al., 2005). In our sample, nearly 30% (n=1005) of patients had PHQ-9 $\geq$ 10 at their entry to the KP. The distribution of PHQ-9 scores represents a wide range of depression severity levels.

The KP collects MS Performance Scales© (PS) (Schwartz et al., 1999) which are patient-reported disability measures. Single-item PS were originally developed for eight domains of function (mobility, hand function, vision, fatigue, cognition, bladder/bowel, sensory, and spasticity) (Chamot et al., 2014). Three more measures were added to the PS in 2001 to assess disability associated with pain, depression, and tremor/coordination (Chamot et al., 2014). Reliability, criterion and construct validity have been established for these domains in previous studies of MS patients (Marrie and Goldman, 2007; Schwartz et al., 1999).

The timed 25-foot walk and 9-hole peg test, are objective performance measures of lower (timed 25-foot walk) and upper (9-hole peg test) extremity function (Polman and Rudick, 2010) The timed 25-foot walk is a test of quantitative mobility and leg function performance, while the 9-hole peg test is a brief, standardized, quantitative test of arm and hand function (Fischer et al., 1999; Rudick et al., 1996; Whitaker et al., 1995).

Anti-depressant treatment (yes or no) is a binary indicator based on whether a patient has a current prescription for one or more anti-depressants. MS disease modifying therapy is a binary indicator based on whether a patient was prescribed a MS disease modifying therapy (Avonex, Betaseron, Extavia, Cellcept, Copaxone, Gilenya, Imuran, Natalizumab, Rebif, or other disease modifying therapy).

Baseline time since MS symptom onset is a measure of disease duration (Poser and Brinar, 2004). MS type at baseline (relapsing or progressive) defines disease phenotype, where progressive forms are characterized by progressive neurologic decline between