Journal of Affective Disorders 188 (2015) 270–277

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The association between latent depression subtypes and remission after treatment with citalopram: A latent class analysis with distal outcome ☆

Christine M. Ulbricht [a,*], Anthony J. Rothschild [b], Kate L. Lapane [a]

[a] Department of Quantitative Health Sciences, University of Massachusetts Medical School, 368 Plantation Street, Worcester 01605, MA, United States
[b] Center for Psychopharmacologic Research and Treatment, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, United States

ARTICLE INFO

Article history:
Received 3 June 2015
Received in revised form
12 August 2015
Accepted 17 August 2015
Available online 1 September 2015

Keywords:
Major depression
Subgroups
Clinical trials
Latent class analysis with distal outcome

ABSTRACT

Background: The objectives were to characterize latent depression subtypes by symptoms, evaluate sex differences in and examine correlates of these subtypes, and examine the association between subtype and symptom remission after citalopram treatment.
Methods: Latent class analysis was applied to baseline data from 2772 participants in the Sequenced Treatment Alternatives to Relieve Depression trial. Indicators were from the Quick Inventory of Depressive Symptomatology. Separate multinomial logistic models identified correlates of subtypes and the association between subtype and the distal outcome of remission. Results: Four latent subtypes were identified: Mild (men: 37%, women: 27%), Moderate (men: 24%, women: 21%), Severe with Increased Appetite (men: 13%, women: 22%), and Severe with Insomnia (men: 26%, women: 31%). Generalized anxiety disorder, bulimia, and social phobia were correlated with Severe with Increased Appetite and generalized anxiety disorder, post-traumatic stress disorder, and social phobia with Severe with Insomnia. Relative to those with the Mild subtype, those with Severe with Increased Appetite (odds ratio$_{men}$ (OR): 0.48; 95% confidence interval (CI): 0.25–0.92; OR $_{women}$: 0.59; 95% CI: 0.41–0.86) and those with Severe Depression with Insomnia (OR$_{men}$: 0.65; 95% CI: 0.41–1.02; OR$_{women}$: 0.45; 95% CI: 0.32–0.64) were less likely to achieve remission.
Limitations: The sample size limited exploration of higher order interactions.
Conclusions: Insomnia and increased appetite distinguished latent subtypes. Sex and psychiatric comorbidities differed between the subtypes. Remission was less likely for those with the severe depression subtypes. Sleep disturbances, appetite changes, and other mental disorders may play a role in the etiology and treatment of depression.

1. Introduction

Major depression is one of the most prevalent, disabling, and costly illnesses worldwide (Kessler et al., 2005a; Whiteford et al., 2013). Despite a 400% increase in antidepressant medication use since 1988, the prevalence of depression remains around 7% for adults in the United States (Kessler et al., 2005b; National Center for Health Statistics, 2011; Substance Abuse and Mental Health Services Administration, 2014). Fewer than half of treated depression patients experience a clinically meaningful reduction in symptoms and uncertainty exists regarding how to successfully obtain symptom remission (Gaynes et al., 2009; Wang and Insel, 2010). Understanding this heterogeneity is necessary to identify predictors of response and ultimately improve depression treatments and services (Insel, 2014).

Depression presents differently by age, gender, race and ethnicity, and psychiatric comorbidities (Alexopoulos, 2005; Kessler, 2003; Rush, 2007; Substance Abuse and Mental Health Services Administration, 2014). This heterogeneity is likely partially explained by the non-specific symptomatology and variability in severity and trajectory of depression. Numerous subtypes have been proposed but clinical utility is limited (Kendler et al., 1996). Identifying homogenous subgroups based on clinically observable characteristics could improve the ability to efficiently predict who will benefit from which treatments (National Advisory Mental Health Council Workgroup, 2010; National Institute of Mental Health, 2015; Simon and Perlis, 2010).

☆Clinical Trial Registration: www.clinicaltrials.gov, NCT00021528.

* Corresponding author.
E-mail address: Christine.Ulbricht@umassmed.edu (C.M. Ulbricht).

http://dx.doi.org/10.1016/j.jad.2015.08.039
0165-0327/

Latent class analysis (LCA) is a person-centered analytic approach which can efficiently identify subgroups comprised of the multiple dimensions of depression (Lanza and Rhoades, 2011). LCA models assume mutually exclusive and exhaustive classes, or subtypes, of individuals within a population differentiated by values of an unobserved categorical latent variable (Collins and Lanza, 2010). This latent variable and the resulting classes are based on observed indicator variables, such as symptoms. Individuals have a probability of membership in each of the latent classes, inferred from response patterns of the indicators (Collins and Lanza, 2010). LCA has been previously used to examine subtypes of major depression in at least 17 published studies, which have differed in regards to participant ascertainment, sample sizes, and the features of depression that have been used to construct the latent subtypes (Li et al., 2014). The results of some of these previous studies have been interpreted as confirming the presence of classic depression subtypes, such as atypical and melancholic depression (Lamers et al., 2012, 2010; Li et al., 2014; Parker et al., 1999; Sullivan et al., 1998). To our knowledge, none of these studies have used LCA with a distal outcome to examine depression subtypes and symptom remission following antidepressant treatment.

We sought to evaluate the extent to which latent subtypes based on depression symptoms could be identified using LCA. Data were used from level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a pragmatic clinical trial of the effectiveness of a variety of treatments for moderate-to-severe nonpsychotic depression (Rush et al., 2004). STAR*D is the largest community-based study of major depression (Trivedi et al., 2006) and had broader eligibility criteria than most depression trials, thus providing a unique opportunity to study patients who would have been excluded from most other studies (Van der Lem et al., 2011; Wisniewski et al., 2009). The objectives were to: examine underlying depression subtypes based on patterns of depression symptoms; evaluate sex differences in these latent depression subtypes; identify correlates of the depression subtypes; and estimate the association between the subtypes and remission.

2. Methods

2.1. Study participants

We used a de-identified dataset from STAR*D. In STAR*D, 4041 treatment-seeking patients were enrolled from 18 primary care and 23 outpatient psychiatric sites between July 2001 and April 2004. (Trivedi et al., 2006). In level 1 of STAR*D, all participants received open-label, flexible dosing of citalopram for 12 weeks (Trivedi et al., 2006). Remission in level 1 was achieved by 27.5% of participants when remission was defined as a score less than or equal to 7 on the 17-item Hamilton Rating Scale of Depression (HRSD) and 32.9% of participantswhen remission was defined as a score less than or equal to 5 on the last observed 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}) (Trivedi et al., 2006). Response was achieved by 47% (secondary outcome: $\geq$50% reduction in QIDS-SR_{16} baseline score) by the end of level 1).

Those who did not respond to citalopram in level 1 had the option of moving to level 2: augmenting citalopram randomly assigned to switch to sertraline, bupropion-SR, or venlafaxine-XR. Psychotherapy was also a treatment option. Participants who did not achieve remission in level 2 could continue to level 3, where they were randomly assigned to mirtazapine or nortriptyline. Participants who did not achieve remission in level 3 could continue to level 4 and be randomly assigned to receive tranylcypromine or venlafaxine-XR with mirtazpine. Approximately half of the participants achieved remission after two levels of treatment (Gaynes et al., 2009).

LCA employs full information maximum likelihood for missing data on indicator variables such as the QIDS-SR_{16} items but requires complete case analysis for missing covariates. Of the evaluable sample (participants with HRSD $\geq$14 at baseline and $\geq$one post-baseline visit, n=2876) (Trivedi et al., 2006), 15 participants were excluded because they were missing all QIDS-SR_{16} indicator items at baseline. An additional 89 participants were excluded because they were missing the covariates of interest, resulting in a sample of 2772 participants for this analysis.

STAR*D participants provided written informed consent after receiving a complete description of the study at enrollment. The protocol was originally approved and monitored by the institutional review boards at the trial's national coordinating center, the data coordinating center, clinical sites, and the Data, Safety, and Monitoring Board of the National Institute of Mental Health. The institutional review board at the University of Massachusetts Medical School determined that this secondary analysis was not human subject research.

2.2. Measures

2.2.1. Indicators of latent subtype membership

The 16 baseline QIDS-SR_{16} items were the indicator variables from which the latent subtype construct was inferred: sad mood, impaired concentration, self-criticism, suicidal ideation, lack of general interest, fatigue, sleep disturbances, appetite and weight changes, and psychomotor agitation/retardation (Rush et al., 2003). Items pertain to experiences in the past seven days, except for weight change (previous two weeks). Item scores ranged from 0 to 3, with scores $\geq$2 indicating the symptom met the DSM-IV depression threshold (Nierenberg et al., 2010). All items were dichotomized ($\leq$1: absence; $\geq$2: presence of a symptom). Although the QIDS-SR_{16} instructions specify that only one item on decreased or increased appetite should be completed, these items were included as separate indicators to capture the direction of change. Weight changes were also treated this way.

2.2.2. Consideration of sex in the LCA

Sex differences occur in depression rates, severity, course, risk factors, and symptoms, with women experiencing depression more often and more severely than men (Kendler and Gardner, 2014; Marcus et al., 2008; Substance Abuse and Mental Health Services Administration, 2014; Young et al., 2009). Sex has also been seen to differentiate the number of latent depression subtypes and the characteristics of subtypes differentiated in other LCAs of depression (Alexandrino-Silva et al., 2013; Rodgers et al., 2014). As such, we did not *a priori* assume that men and women would have the same subtypes of depression. Instead, we evaluated: 1) if men and women experienced the same types of depression; and 2) sex differences in subtype prevalences.

2.2.3. Correlates of depression subtype membership

We considered sociodemographic and clinical variables as correlates of depression subtype membership. Baseline age ($<$ 45 years versus $\geq$45 years), race, and psychiatric comorbidities were considered because these are previously identified demographic and clinical predictors of depression subtypes (Bühler et al., 2014). Comorbid DSM-IV conditions were assessed at baseline with the Psychiatric Diagnostic Screening Questionnaire (Zimmerman, 2002), which screens for 13 mood, anxiety, eating, substance use, and somatoform disorders. A threshold of 90% specificity was used to determine the presence of a disorder (Rush et al., 2005). We examined comorbid post-traumatic stress disorder (PTSD), social phobia, generalized anxiety disorder (GAD), and bulimia because