Association of depression symptom network structure with early-relapse in opioid-dependent individuals treated with extended-release naltrexone or buprenorphine-naloxone

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Introduction

Depressive disorders are heterogeneous conditions that commonly co-occur with opioid use disorder (OUD) and have complex relationships with OUD treatment outcomes.[1,2] Some of the variance in this association may be due to relationships between opioid use and specific depressive symptoms or symptom clusters that are more impactful on OUD treatment course and relapse risk. Recently, novel network approaches have emerged that conceptualize psychiatric disorders as complex dynamic systems of mutually interacting symptoms.[3] Applying these network approaches to the study of co-occurring disorders may improve our understanding of the how substance use and psychiatric symptoms independently and interactively contribute to prognosis.[3-5]

Objectives

In the present study, we examined associations between baseline depression and OUD symptom network structures and early relapse to opioids in opioid-dependent adults randomized to receive one of two commonly prescribed, pharmacologically-distinct medications - extended-release naltrexone (XR-NTX), an opioid antagonist, and sublingual buprenorphine-naloxone (BUP-NAL), a partial opioid agonist.

Methods

Overview. Associations between depressive symptom network structure and opioid relapse were examined using data from a 24-week open-label, randomized controlled, comparative effectiveness study comparing XR-NTX versus BUP-NAL for opioid relapse prevention (NIDA CTN-0051).[6]

Participants. In the study, 570 opioid-dependent adults (169 females, mean age = 33.9 years) were randomly assigned to 24-weeks of XR-NTX (4ml, 380 mg naltrexone base IM every 4 weeks) or Bup/Nal (SL, daily dose range = 8-24 mg), with both treatment arms offered weekly behavioral therapy. XR-NTX and BUP-NAL groups did not differ in age, sex, education, or on baseline (bsl) depression.

Measures. Depressive symptoms were assessed via the 17-item Hamilton Depression Scale (HAM-D). DSM-5 OUD diagnosis and severity was assessed based upon presence (yes vs. no) of each of the 11 symptoms from the Addiction Severity Index-Lite.

Data analysis. Sparse network structure of the 17 HAM-D depressive symptoms along with OUD total symptom count (severity) at bsl were estimated using Gaussian models of regularized partial correlations and LASSO. Global and local connectivity of network structures were compared across early-relapsers (n=96) and successful inductors (n=474) using permutation testing.

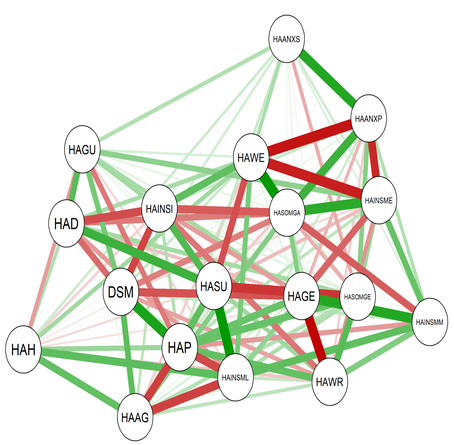
Results

26% of participants met criteria for moderate-to-severe MDD. 204 [72%] of 283 participants in the XR-NTX group and 270 [94%] of 287 in the BUP-NAL group were early-relapsers. The depressive symptom network of early-relapsers was more strongly connected than that of successful inductors (see **Fig.'s 1a** and **2a**.). In the resulting bsl depression network of early-relapsers, *psychomotor, suicidality, somatic gastrointestinal (GI)-, and somatic genital-symptoms* were the 4 most central symptoms across all centrality indices (strength [see **Fig's. 1b** and **2b**], closeness, and betweeness). In contrast, while *psychomotor symptoms* were also central in the bsl depression network of successful inductors, other depressive symptoms were weakly connected and the global symptom network was more sparse. In examining temporal stability of networks, we found that the network structures became sparser and less strongly connected over the 24-week treatment course in both early-relapsers and successful inductors.

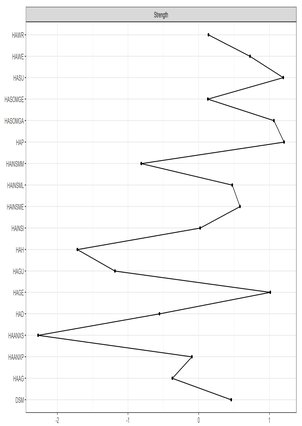
Figures 1 and 2. Baseline depression symptom networks and centrality plots for opioid dependent individuals stratified by early-relapse status

Early Relapsers – Baseline (n = 96)

1a. Depression symptom network

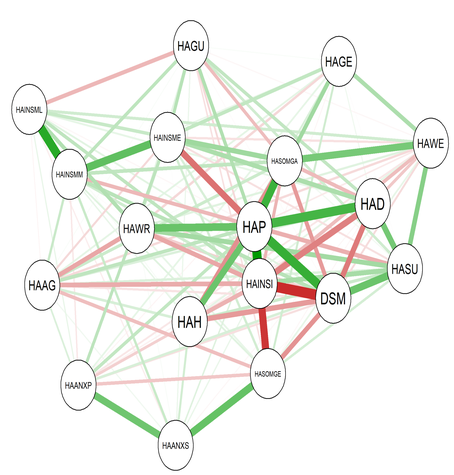


1b. Centrality Plot

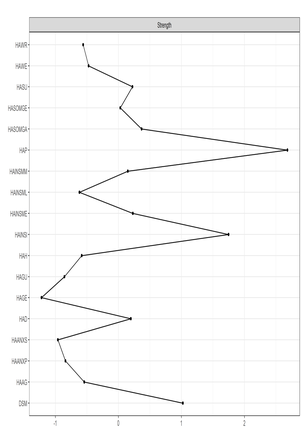


Successful Inductors- Baseline (n = 474)

2a. Depression symptom network



2b. Centrality Plot



Legend 1. Symptom Nodes

HADPMOOD	Depressed Mood	**HAANXYPSY**	Anxiety- Psychic
HAGUILT	Feelings of Guilt	**HAANXSOM**	Anxiety- Somatic
HASUICDE	Suicide	**HASOMGAS**	Somatic Symptoms- GI
HAINSMER	Insomnia- Early	**HAGENSYM**	Genital Symptoms
HAINSMMD	Insomnia- Middle	**HAHYPOCH**	Hypochondriasis
HAINSMLT	Insomnia- Late	**HAWEIGHT**	Loss of Weight
HAWRKACT	Work and Activities	**HAINSIGT**	Insight
HAPSYCHM	Retardation	**DSM5OUDSEV**	OUD Severity
HAAGITAN	Agitation		

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Conclusion

Our findings indicate that the connectivity of depression symptom networks in opioid-dependent individuals are related to longitudinal course of opioid use and early-relapse to opioids during medication assisted treatment for OUDs. Specifically, we found that early-relapsers exhibited a more densely connected depression symptom networks at baseline compared to successful inductors and depressive symptoms of *suicidality* and *somatization* showed large between-group differences. While these findings should be interpreted cautiously and require replication, our preliminary results suggest that depression symptom network structure and specific depressive symptom clusters may carry prognostic significance for OUD and co-occurring depression.

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