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Original investigation

The Network Structure of Tobacco Withdrawal in a Community Sample of Smokers Treated With Nicotine Patch and Behavioral Counseling

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Abstract

Introduction: Network theories of psychopathology highlight that, rather than being indicators of a latent disorder, symptoms of disorders can causally interact with one another in a network. This study examined tobacco withdrawal from a network perspective.

Methods: Participants (n = 525, 50.67% female) completed the Minnesota Tobacco Withdrawal Scale four times (2 weeks prior to a target quit day, on the target quit day, and 4 and 8 weeks after the target quit day) over the course of 8 weeks of treatment with nicotine patch and behavioral counseling within a randomized clinical trial testing long-term nicotine patch therapy in treatment-seeking smokers. The conditional dependence among seven withdrawal symptoms was estimated at each of the four measurement occasions. Influential symptoms of withdrawal were identified using centrality indices. Changes in network structure were examined using the Network Comparison Test.

Results: Findings indicated many associations among the individual symptoms of withdrawal. The strongest associations that emerged were between sleep problems and restlessness, and associations among affective symptoms. Restlessness and affective symptoms emerged as the most central symptoms in the withdrawal networks. Minimal differences in the structure of the withdrawal networks emerged across time.

Conclusions: The cooccurrence of withdrawal symptoms may result from interactions among symptoms of withdrawal rather than simply reflecting passive indicators of a latent disorder. Findings encourage greater consideration of individual withdrawal symptoms and their potential interactions and may be used to generate hypotheses that may be tested in future intensive longitudinal studies.

Implications: This study provides a novel, network perspective on tobacco withdrawal. Drawing on network theories of psychopathology, we suggest that the cooccurrence of withdrawal symptoms may result from interactions among symptoms of withdrawal over time, rather than simply reflecting passive indicators of a latent disorder. Results indicating many associations among individual

symptoms of withdrawal are consistent with a network perspective. Other results of interest include minimal changes in the network structure of withdrawal across four measurement occasions prior to and during treatment with nicotine patch and behavioral counseling.

Introduction

Cigarette smoking remains a leading cause of morbidity and mortality worldwide.[1] Upon smoking cessation or reduction, withdrawal symptoms (including anxiety, difficulty concentrating, and restlessness) appear that serve as primary determinants of smoking continuation and reuptake.[2–4] Despite the availability of interventions to successfully target withdrawal symptoms,[5] quitting smoking is notoriously difficult, with the majority of even the most intensive intervention-guided cessation attempts ending in relapse.[6,7] Here, we aim to gain novel insights into tobacco withdrawal by conceptualizing withdrawal as a network of interacting symptoms.

Symptoms of withdrawal are traditionally treated as passive indicators of an underlying syndrome.[8] During diagnosis with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-V*[9]), for example, if a patient meets four or more withdrawal symptoms (anger, anxiety, depressed mood, difficulty concentrating, increased appetite, insomnia, and restlessness), then criteria for tobacco withdrawal are met. From this perspective, the indicators of withdrawal (the individual symptoms) are exchangeable with one another such that endorsing any four or more symptoms results in a diagnosis of withdrawal. This approach to withdrawal seems to have some validity. For example, greater withdrawal severity, operationalized by aggregating information on the experiences of individual withdrawal symptoms, is associated with smoking relapse.[10,11]

A network approach to tobacco withdrawal provides a complementary but alternative way of conceptualizing withdrawal. Network theories of psychopathology highlight the intuitive notion that, rather than being indicators of a latent disorder, symptoms of disorders interact, forming networks of causally connected symptoms.[12–14] Individual symptoms take on important roles in their own right. From this perspective, tobacco withdrawal would be seen as a network in which the nodes of the network represent symptoms and the edges represent associations among symptoms. In this symptom network, symptoms are associated with one another, not simply because they share the common cause of the latent syndrome of withdrawal, but because they interact with one another over time.

The interaction among symptoms from a network perspective is intuitive and is reflected in empirical research. Studies that capture dense time-series of symptoms as participants go about their daily lives and that allow the examination of moment-to-moment associations among constructs[15,16] highlight potentially causal interactions among symptoms that fall under the purview of withdrawal. Particularly salient examples include lagged, moment-to-moment associations among depressed mood and anxiety, in which levels of depressed mood at previous timepoints predict levels of anxiety at the next timepoint.[17,18] Other relevant examples include laboratory studies that have revealed increases in appetite[19] and greater difficulty concentrating[20] following sleep restriction, again indicating causal associations among constructs considered to be withdrawal symptoms.

The network perspective of psychopathology has been applied to a range of psychopathologies to date, including major depressive disorder,[21] schizotypal personality disorder,[22] posttraumatic stress disorder,[23] psychotic disorder,[24] and autism and obsessive compulsive disorder.[25] Notably, the network perspective has been extended to examine associations among symptoms of substance abuse and dependence.[26] Although this particular examination included withdrawal in the network, the study treated withdrawal as a symptom rather than examining individual symptoms of withdrawal, an examination that was beyond the scope of measures included in the study. A number of recent empirical findings support the plausibility and potential utility of a network perspective for understanding tobacco withdrawal. The network perspective emphasis on the importance of considering individual symptoms is in line with findings that different symptoms of withdrawal exhibit different time courses across both short (ie, minutes post-cessation[27]) and long (ie, weeks[28]) timescales. Further, smoking cessation treatments have opposing effects on different symptoms of tobacco withdrawal (eg, difficulty concentrating decreases while appetite increases on varenicline[29]). Differences in the time courses and response to treatment of individual withdrawal symptoms suggest that individual symptoms might not be exchangeable with one another, thus necessitating a greater consideration of the individual symptoms that make up the latent construct of tobacco withdrawal.

In addition to findings highlighting the importance of considering individual symptoms, studies provide preliminary support for the network perspective's proposal that individual withdrawal symptoms interact with one another in a potentially causal manner over time.[30] Recent work in experience sampling, for example, considered the dynamic relations among cessation fatigue, negative affect, nicotine craving, and self-efficacy.[31] Taking a complex systems approach, this work showed that these four constructs changed over time in response to each other during the course of smoking cessation, encouraging further work in the analysis of the network structure of tobacco withdrawal.

To examine the potential utility of a network perspective on tobacco withdrawal, we use network modeling techniques to estimate the network structure of tobacco withdrawal symptoms in a sample of tobacco smokers receiving treatment with a nicotine patch and behavioral counseling. We provide novel insights into how individual withdrawal symptoms relate to one another and generate hypotheses about the causal interactions among individual symptoms that may be tested in future work using the repeated measurement of individual withdrawal symptoms over short periods of time. Using data from four timepoints during a clinical trial, we also provide insight into the stability of the network structure of tobacco withdrawal over the course of several weeks in the context of changes in tobacco use.

Method

We made use of data from a randomized clinical trial (ClinicalTrials.gov Identifier: NCT01047527) designed to provide insight into the therapeutic benefit of long-term nicotine patch therapy in treatment-seeking smokers.[32]

Participants

Participants (n = 525; 50.67% female; Supplementary Table 1) were recruited from June 22, 2009, to April 15, 2014. Participants were

eligible if they met three criteria: (1) were 18 years of age or older, (2) smoked at least 10 cigarettes per day, and (3) were interested in smoking cessation. Exclusion criteria included the following: (1) experiencing a current medical problem for which transdermal nicotine therapy is contraindicated (eg, latex allergy), (2) had a lifetime *DSM* (Fourth Edition[33]) diagnosis of psychotic or bipolar disorder, (3) had current suicidality identified by the Mini-International Neuropsychiatric Interview[34], and (4) were unable to communicate in English. Women were excluded if they were pregnant, planning a pregnancy, or lactating. Written informed consent was obtained from all study participants. To control for variability attributable to treatment duration, the present analyses included only data from the first 12 weeks of the study during which time all participants were given open-label transdermal nicotine.

Procedures

After an in-person visit to confirm eligibility, participants were randomized to 8, 24, or 52 weeks of therapy consisting of transdermal nicotine patches delivering a dose of 21 mg (Nicoderm CQ; GlaxoSmithKline). All participants received behavioral smoking cessation counseling consistent with guidelines from the US Public Health Service.[35] During the first 8 weeks of this trial, participants underwent an in-person prequit counseling at baseline (week 2), which focused on preparing for cessation, and then set a smoking cessation date for week 0, at which time they were instructed to start using the patch. At weeks 4 and 8, participants received telephone counseling that focused on managing urges and triggers to smoking and developing strategies to avoid relapse. Assessments (eg, of withdrawal) were conducted at the prequit session (week 2) and at weeks 0, 4, and 8 by telephone.

Measures

At the prequit session, participants completed self-report measures of demographic (eg, age, race, sex) and smoking-related (cigarettes per day, the Fagerström Test for Cigarette Dependence score[36]) variables. To capture tobacco withdrawal, we used the Minnesota Tobacco Withdrawal Scale (MTWS[37]) at the prequit, 0-, 4-, and 8-week assessments. The MTWS is a 15-item scale. The seven items of the scale that reflect the *DSM-V* criteria for tobacco withdrawal were anger, anxious or nervous, depressed mood, difficulty concentrating, increased appetite, insomnia, and restlessness. The seven items were measured on an ordinal scale: 0, *none*; 1, *slight*; 2, *mild*; 3, *moderate*; 4, *severe*.

Data Analysis

Data analysis scripts and zero-order polychoric correlations among the MTWS items at each occasion are available as Supplementary Material. To examine the network structure of tobacco withdrawal symptoms, we analyzed complete data available from the MTWS at the prequit (n = 523), 0-week (n = 496), 4-week (n = 457), and 8-week (n = 426) assessments. At these assessments, all participants were undergoing the same procedures and, thus, data from the treatment groups could be combined to reach sample sizes appropriate for the network analysis undertaken in this study. For each assessment, we estimated a tobacco withdrawal network using a Gaussian graphical model[38,39]. In this model, nodes represent individual symptoms of tobacco withdrawal. Nodes are connected by undirected edges indicating conditional dependence between two symptoms. The input to the Gaussian graphical model was a covariance matrix. Because the data were ordinal, we used polychoric correlations. The use of the Gaussian graphical model entails the estimation of many parameters. To avoid obtaining false-positive associations among symptoms, we used a regularization approach—the graphical least absolute shrinkage and selection operator—to shrink all edge weights, setting many to zero.[40] This approach mitigates the problem of estimating spurious associations and results in a sparse network structure.

To assess the accuracy of the network estimation, we tested the edge-weight accuracy. Edge-weight accuracy was estimated using nonparametric bootstrapping with 1000 samples using the R package *bootnet*. The edge-weight bootstrapped confidence intervals should not be interpreted as significance tests to zero in the context of the regularization approach. The least absolute shrinkage and selection operator regularization approach is sufficiently conservative for determining whether an edge is strong enough to be included in the network.[39] Instead, the confidence intervals provide insight into the accuracy of edge-weight estimates and may be used to compare edges to one another by examining the overlap of estimated confidence intervals. After obtaining these estimates, we tested for differences in edge weights using a bootstrap edge difference test with 1000 bootstrap samples.[39]

To provide additional insight into the network structure of tobacco withdrawal, we estimated centrality indices. Nodes with high centrality have strong connections to many other nodes and connect otherwise disparate nodes to one another. As such, they are theorized to be particularly influential in the development and maintenance of mental disorders.[12,21] Three centrality indices we examined were node strength, closeness centrality, and betweenness centrality. Node strength quantifies the extent to which a node is directly connected to other nodes. Closeness centrality quantifies the extent to which a node is indirectly connected to other nodes. Betweenness centrality quantifies the extent to which a node lies on shortest topological paths between other nodes.

We investigated the stability of the order of centrality indices based on subsets of the data. This approach indicates the extent to which the order of centrality indices remains the same after reestimating the network with fewer cases (ie, an *m out of n bootstrap*[41] with 1000 samples). By examining the extent to which the correlation changes after dropping cases, we can achieve insight into the extent to which interpretations of centrality indices may be prone to error. In addition, a correlation stability coefficient was estimated. This coefficient represents the maximum proportion of cases that can be dropped such that, with 95% probability, the correlation between the original centrality indices and centrality networks based on subsets of the data is 0.7 or higher. The value of 0.7 is a default value chosen as it indicates a large effect. Guidelines for correlation stability coefficients that are sufficiently large for centrality indices to be interpretable suggest values greater than 0.25 and, preferably, greater than 0.50.[39] We then tested for differences in node centrality using a centrality bootstrapped difference test with 1000 bootstrap samples.[39]

To investigate differences in the structure of the tobacco withdrawal network across the four assessment periods, we used a permutation-based hypothesis test named the Network Comparison Test[42] using 1000 iterations. We tested for differences in network structure and global strength between all possible pairs of measurement occasions. The network structure invariance test examines whether the network structure is indistinguishable across measurement occasions. The global strength invariance test examines

whether the overall level of connectivity is indistinguishable across measurement occasions. We repeated these tests using only participants with data for all four of the assessment occasions (n = 403).

We conducted a number of statistical analyses to determine if missing data patterns were associated with any of the demographic variables of interest. Independent sample t tests revealed that participants with missing data were more likely to be younger than participants with complete data, $t(178.53) = -3.51$, $p = .001$, and more likely to have a shorter duration of smoking in years, $t(190.13) = -3.49$, $p = .001$, but did not differ on their Fagerström Test for Nicotine Dependence score, age of smoking initiation, or average cigarettes smoked per day (all p values > .05). Chi-square tests indicated that participants with missing data were more likely to be white than participants with complete data, $\chi^2(1) = 5.68$, $p = .02$, but did not differ in gender, marital status, sexual orientation, education level, income, current or past depression, or current substance dependence or abuse (all p values > .05).

Results

The estimated networks of the associations among tobacco withdrawal symptoms at each of the four assessments are shown in Figure 1 (see Supplementary Tables 2–5 for the adjacency matrices). At each assessment, symptoms of tobacco withdrawal were highly interconnected. Of 21 potential edges, the number of nonzero edges ranged from 15 to 18 across all four networks. Most edges were positive (depicted in blue), indicating that when participants experienced high levels of a symptom they were likely to show high values of another symptom. Two negative edges (depicted in red) were observed in the week 4 symptom networks only, indicating that participants with greater sleep problems experienced less anger and that participants with increased appetites had less difficulty concentrating at this assessment. The edge between sleep problems and anxiety was estimated as zero across all four assessments.

To determine the specificity of our findings, we investigated the accuracy of the estimated edge weights in the tobacco withdrawal network. Edge-weight bootstrapped confidence intervals are presented in Supplementary Figure 1. The edge-weight bootstrap revealed that the networks were moderately accurately estimated. There is considerable overlap among the 95% confidence intervals of the edge weights. As such, interpreting the order of edges in the network should be done cautiously. Results of the edge-weight bootstrapped difference test (Supplementary Figure 2) indicated that the edge between restlessness and sleep problems was particularly strong, significantly stronger than all other edges at the prequit, week 4, and week 8 assessments, and stronger than all but one edge (the anger-depressed mood edge) at the week 0 assessment. Associations among the affective symptoms (ie, anger, anxiety, and depressed mood) also tended to be high.

To identify tobacco withdrawal symptoms that might be particularly influential within each network, we computed centrality indices. The betweenness centrality, closeness centrality, and strength of each symptom at each assessment are displayed in Supplementary Figure 3. We investigated the stability of the centrality indices using an m out of n bootstrap. The results are shown in Supplementary Figure 4. Correlation stability coefficients indicate that the proportion of cases that could be dropped from the sample while retaining a 95% probability of obtaining a correlation of 0.7 or higher between the original centrality estimates and the centrality estimates from a subsample were 0.05 for betweenness centrality, 0.21 for closeness centrality, and 0.67 for strength for the prequit assessment; 0.00 for betweenness centrality, 0.36 for closeness centrality, and 0.52 for strength for the week 0 assessment; 0.21 for betweenness centrality, 0.52 for closeness centrality, and 0.67 for strength for the week 4 assessment; and 0.00 for betweenness centrality, 0.36 for closeness centrality, and 0.52 for strength for the week 8 assessment. Thus, stability of the centrality indices was least stable for betweenness centrality and most stable for strength. The correlation stability coefficient for betweenness centrality did not meet the recommended value of 0.25 or greater at any assessment. The correlation stability coefficient for closeness centrality was acceptable at three of the four waves. Only the correlation stability coefficient for strength centrality was acceptable at each wave, exhibiting values greater than the more conservative cutoff of 0.50.

Given the acceptable correlation stability coefficients for strength centrality, we performed centrality bootstrapped difference tests on strength centrality only (Supplementary Figure 5). Restlessness emerged as having particularly high strength centrality, especially in prequit, week 0, and week 4 assessments. Affective symptoms (particularly depressed mood and anxiety) also exhibited high strength centrality values. Increased appetite was consistently estimated as the least central symptom.

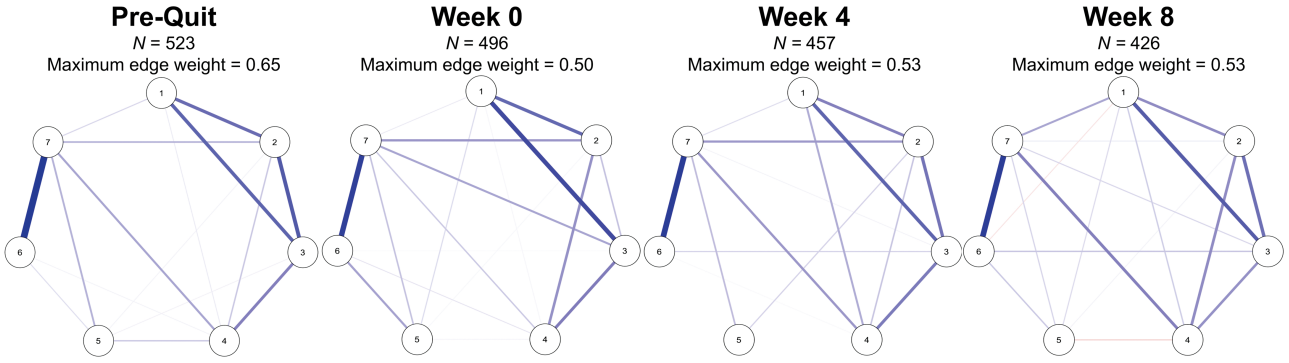

Figure 1. The network structure of the seven tobacco withdrawal symptoms at each assessment. Blue edges represent positive associations among symptoms. Red edges represent negative associations. The network structure is estimated using a Gaussian graphical model. Each edge represents partial correlation coefficients between two variables after conditioning on all other variables. The size and transparency of the edges reflect the magnitude of the association between two symptoms, with the thickest edge set to a maximum of 0.65 across all four networks to facilitate comparisons across measurement occasions. Nodes were placed in a circular layout in order to facilitate visual comparison across assessments.

To examine differences in networks across the assessment periods, we conducted pairwise Network Comparison Tests of network structure and global connectivity invariance. Tests of network structure invariance and global strength invariance indicated no significant differences in network structure or global strength (all p values > .05; Supplementary Figures 6–9). This result suggests that the structure of tobacco withdrawal networks is relatively stable prior to and during nicotine patch therapy.

Discussion

The majority of even the most intensive intervention-guided cessation attempts end in relapse,[6,7] necessitating novel approaches to understanding the barriers to smoking cessation. The present study applied a network perspective to tobacco withdrawal in which the associations among individual symptoms of withdrawal were of interest rather than being treated as indicators of a latent tobacco withdrawal syndrome. Consistent with the notion of tobacco withdrawal as a network of interdependent symptoms, findings indicated many associations among the individual symptoms of withdrawal in the context of treatment involving nicotine patch and behavioral counseling.

Of 21 potential symptom associations at each assessment, between 15 and 18 associations emerged in the graphical model. The strongest association was between sleep problems and restlessness, and associations among affective symptoms. These associations provide insight into symptoms that cooccur within participants. Participants experiencing sleep problems were likely to be experiencing restlessness, and participants experiencing depressed mood were likely to be experiencing anxiety. We also interpret the edges in the withdrawal symptom networks as providing insight into putative causal associations. For example, we hypothesize that the association among anxiety and depressed mood indicates potential causal pathways from anxiety to depressed mood, depressed mood to anxiety, or both. Such hypotheses are consistent with broader theories of the dynamic associations among emotions[43] and empirical research indicating the presence of such dynamics beyond the tobacco withdrawal literature.[44]

Our examination of the centrality of the estimated withdrawal networks allowed identification of symptoms that might be particularly influential on the experience of withdrawal. Symptoms with high centrality are thought to play a role in triggering the development of other symptoms because of their associations with many other symptoms.[21] Betweenness centrality and closeness centrality did not reach acceptable levels of stability. As such, we focused on strength centrality. Restlessness and affective symptoms, particularly depressed mood and anxiety, emerged as the symptoms with the highest strength centrality in the withdrawal networks and, thus, might make particularly useful clinical targets,[45] although the role for central symptoms as promising clinical targets remains controversial.[46]

The availability of data at four assessment timepoints allowed an examination of the stability of withdrawal networks across changes in tobacco use in the context of nicotine patch and behavioral counseling treatments. Minimal differences in the edge weights of the four networks emerged. Future work considering withdrawal networks during smoking cessation attempts in the absence of nicotine patch and behavioral counseling will allow an examination of the extent to which the treatment that participants underwent during a cessation attempt was implicated in network stability. An alternative possibility is that the network structure of withdrawal is stable across levels of smoking satiety and that it is the levels of symptoms that change along with levels of satiety. Stability in network structure in the context of marked changes in psychopathology severity has been observed in the context of major depressive disorder[47] and reminds us that, although the network approach provides insight into the covariance of symptoms, little information about symptom levels is captured in this approach.[48] We anticipate that future efforts capturing both covariance among symptoms as well as symptom levels within an annotated graph structure will overcome this current limitation of symptom networks.[49,50]

To date, withdrawal symptoms have been treated as passive indicators of an underlying syndrome. From this perspective, the cooccurrence of symptoms within individuals results from an unobserved, latent entity. The alternative and complementary perspective presented here suggests that the cooccurrence of symptoms may result from interactions among individual symptoms of withdrawal. Both perspectives provide useful descriptions of observed data[51] yet the substantive implications of a latent variable versus a network perspective differ drastically. Chiefly, from the network perspective, treatment might focus on minimizing the connections between individual symptoms across time because the interplay between symptoms, an aspect not captured in formative models of withdrawal, may impact the emergence and maintenance of withdrawal. The presence of strong connections between symptoms across time increases the ease with which activity associated with individual symptoms propagates through a symptom network, potentially resulting in a self-perpetuating network of interdependent states. Indeed, patients with densely interconnected symptom networks in domains outside tobacco withdrawal show greater vulnerability to developing psychopathology,[52] are more likely to be currently experiencing more severe symptoms of psychopathology,[18] and are more likely to be in the process of transitioning to a psychopathological state[53] relative to participants with less dense symptom networks. The findings presented here suggest the promise of a network perspective of tobacco withdrawal that places an emphasis on symptom interactions, and of future studies using intensive repeated measures designs to capture the interactions among individual symptoms on short timescales.[54]

Limitations and Future Directions

The findings should be interpreted in light of a number of limitations. Participants were enrolled in a smoking cessation trial involving nicotine patch and the resulting network structure may not generalize beyond the current sample and design, necessitating the analysis of data from more representative samples of tobacco smokers undergoing different withdrawal experiences. However, as the data were from an effectiveness trial with limited inclusion and exclusion criteria, the results have fairly broad generalizability to the population of smokers interested in quitting smoking. Although the networks estimated represent putative causal associations among withdrawal symptoms, strong conclusions about the dynamic nature of the associations among individual symptoms may not be drawn until repeated measures approaches are used that can more fully articulate within-person processes. Finally, the Network Comparison Test that we used to examine potential differences in edge weights across the networks estimated at each assessment is suited for Gaussian and binary data. As our data were ordinal, the results from this test should be interpreted with caution. However, Spearman correlations of the edge lists on networks estimated using Pearson and polychoric correlations were highly similar at all four occasions (all r values >.96; see also Forbes *et al.*[55]).

Conclusions

This study is the first to our knowledge to examine the network structure of tobacco withdrawal symptoms. Findings are consistent with the concept of tobacco withdrawal as a complex network of cognition, affect, and behavior. Particularly strong associations emerged between sleep problems and restlessness and among affective symptoms (anger, anxiety, and depressed mood). Restlessness and affective symptoms (in particular depressed mood and anxiety) were especially central to the network architecture. The findings encourage greater consideration of individual symptoms and their potential interaction and can be used to generate hypotheses about the associations among symptoms over time that may be tested in repeated measures designs.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

BH and RS report receiving varenicline (Chantix) and placebo free of charge from Pfizer for use in ongoing National Institutes of Health–supported clinical trials. RS reports having provided consultation to Pfizer and GlaxoSmithKline. BH reports having provided consultation for Pfizer. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. American Cancer Society. *Cancer Facts and Figures 2010*. Atlanta, GA: American Cancer Society; 2010.
2. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychol Rev.* 2004;111(1):33–51.
3. Piper ME. Withdrawal: expanding a key addiction construct. *Nicotine Tob Res*. 2015;17(12):1405–1415.
4. Solomon RL, Corbit JD. An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychol Rev.* 1974;81(2):119–145.
5. Aveyard P, Raw M. Improving smoking cessation approaches at the individual level. *Tob Control.* 2012;21(2):252–257.
6. Alterman AI, Gariti P, Mulvaney F. Short- and long-term smoking cessation for three levels of intensity of behavioral treatment. *Psychol Addict Behav.* 2001;15(3):261–264.
7. Fiore MC, Bailey WC, Cohen SJ. *Treating Tobacco Use and Dependence: Clinical Practice Guideline*. Rockville, MD: U.S. Department of Health and Human Services, U.S. Public Health Service; 2000.
8. Toll BA, O'Malley SS, McKee SA, Salovey P, Krishnan-Sarin S. Confirmatory factor analysis of the Minnesota Nicotine Withdrawal Scale. *Psychol Addict Behav.* 2007;21(2):216–225.
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
10. Kenford SL, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Predicting relapse back to smoking: contrasting affective and physical models of dependence. *J Consult Clin Psychol.* 2002;70(1):216–227.
11. Piasecki TM, Jorenby DE, Smith SS, Fiore MC, Baker TB. Smoking withdrawal dynamics: II. Improved tests of withdrawal-relapse relations. *J Abnorm Psychol.* 2003;112(1):14–27.
12. Borsboom D, Cramer AO. Network analysis: an integrative approach to the structure of psychopathology. *Annu Rev Clin Psychol.* 2013;9(1): 91–121.
13. Bringmann LF, Vissers N, Wichers M, et al. A network approach to psychopathology: new insights into clinical longitudinal data. *PLoS One.* 2013;8(4):e60188.
14. Schmittmann VD, Cramer AO, Waldorp LJ, et al. Deconstructing the construct: a network perspective on psychological phenomena. *New Ideas Psychol.* 2013;31(1):43–53.
15. Larson R, Csikszentmihalyi M. The experience sampling method. In: H.T. Reis ed. *New Directions for Methodology of Social and Behavioral Sciences*. vol. 15. San Francisco, CA: Jossey-Bass; 1983:41–56.
16. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol.* 2008;4(1):1–32.
17. Lydon-Staley DM, Xia M, Mak HW, et al. Adolescent emotion network dynamics in daily life and implications for depression. *J Abnorm Child Psychol*. 2018; doi:10.1007/s1080.
18. Pe ML, Kircanski K, Thompson RJ, et al. Emotion-network density in major depressive disorder. *Clin Psychol Sci.* 2015;3(2): 292–300.
19. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141(11):846–850.
20. Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. *Pain.* 2005;119(1-3):56–64.
21. Fried EI, Epskamp S, Nesse RM, Tuerlinckx F, Borsboom D. What are "good" depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *J Affect Disord.* 2016;189(1):314–320.
22. Fonseca-Pedrero E, Ortuño J, Debbané M, et al. The network structure of schizotypal personality traits. *Schizophr Bull.* 2018;44(suppl 2):S468–S479.
23. Sullivan CP, Smith AJ, Lewis M, Jones RT. Network analysis of PTSD symptoms following mass violence. *Psychol Trauma*. 2018;10(1):58–66.
24. Isvoranu AM, van Borkulo CD, Boyette LL, Wigman JT, Vinkers CH, Borsboom D; Group Investigators. A network approach to psychosis: pathways between childhood trauma and psychotic symptoms. *Schizophr Bull.* 2017;43(1):187–196.
25. Ruzzano L, Borsboom D, Geurts HM. Repetitive behaviors in autism and obsessive-compulsive disorder: new perspectives from a network analysis. *J Autism Dev Disord*. 2015;45(1):192–202.
26. Rhemtulla M, Fried EI, Aggen SH, Tuerlinckx F, Kendler KS, Borsboom D. Network analysis of substance abuse and dependence symptoms. *Drug Alcohol Depend*. 2016;161(1):230–237.
27. Hendricks PS, Ditre JW, Drobes DJ, Brandon TH. The early time course of smoking withdrawal effects. *Psychopharmacology (Berl)*. 2006;187(3):385–396.
28. West RJ, Hajek P, Belcher M. Time course of cigarette withdrawal symptoms during four weeks of treatment with nicotine chewing gum. *Addict Behav.* 1987;12(2):199–203.

29. Foulds J, Russ C, Yu CR, et al. Effect of varenicline on individual nicotine withdrawal symptoms: a combined analysis of eight randomized, placebo-controlled trials. *Nicotine Tob Res*. 2013;15(11):1849–1857.
30. Cook JW, Lanza ST, Chu W, Baker TB, Piper ME. Anhedonia: its dynamic relations with craving, negative affect, and treatment during a quit smoking attempt. *Nicotine Tob Res*. 2017;19(6):703–709.
31. Bekiroglu K, Russell MA, Lagoa CM, Lanza ST, Piper ME. Evaluating the effect of smoking cessation treatment on a complex dynamical system. *Drug Alcohol Depend*. 2017;180(1):215–222.
32. Schnoll RA, Goelz PM, Veluz-Wilkins A, et al. Long-term nicotine replacement therapy: a randomized clinical trial. *JAMA Intern Med*. 2015;175(4):504–511.
33. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
34. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(suppl 20):22–33;quiz 34.
35. Fiore MC, Jaen CR, Baker T, et al. *Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: US Public Health Service. US Public Health Service Clinical Practice Guideline; 2008.
36. Fagerström K. Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence. *Nicotine Tob Res*. 2012;14(1):75–78.
37. Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. *Exp Clin Psychopharmacol*. 1999;7(4):354–361.
38. Lauritzen SL. *Graphical Models*. Oxford, UK: Clarendon Press; 1996.
39. Epskamp S, Fried EI. A tutorial on regularized partial correlation networks. *Psychol Methods*. 2018. Advanced online publication. doi:10.1037/met0000167
40. Epskamp S, Cramer AO, Waldorp LJ, et al. qgraph: network visualizations of relationships in psychometric data. *J Stat Softw*. 2012;48(4): 1–18.
41. Chernick MR. *Bootstrap Methods: A Guide for Practitioners and Researchers*. New York: Wiley; 2011.
42. van Borkulo C, Boschloo L, Borsboom D, Penninx BW, Waldorp LJ, Schoevers RA. Association of symptom network structure with the course of [corrected] depression. *JAMA Psychiatry*. 2015;72(12):1219–1226.
43. Gross JJ, Muñoz RF. Emotion regulation and mental health. *Clin Psychol*. 1995;2(2):151–164.
44. Pe ML, Kuppens P. The dynamic interplay between emotions in daily life: augmentation, blunting, and the role of appraisal overlap. *Emotion*. 2012;12(6):1320–1328.
45. Boschloo L, van Borkulo CD, Borsboom D, Schoevers RA. A prospective study on how symptoms in a network predict the onset of depression. *Psychother Psychosom*. 2016;85(3):183–184.
46. Fried EI, Cramer AOJ. Moving forward: challenges and directions for psychopathological network theory and methodology. *Perspect Psychol Sci*. 2017;12(6):999–1020.
47. Snippe E, Viechtbauer W, Geschwind N, Klippel A, de Jonge P, Wichers M. The impact of treatments for depression on the dynamic network structure of mental states: two randomized controlled trials. *Sci Rep*. 2017;7(1): 46523.
48. Bringmann LF, Eronen MI. Don't blame the model: reconsidering the network approach to psychopathology. *Psychol Rev*. 2018;125(4):606–615.
49. Murphy AC, Gu S, Khambhati AN, et al. Explicitly linking regional activation and functional connectivity: community structure of weighted networks with continuous annotation. *arXiv preprint*. 2016; arXiv:1611.07962.
50. Newman ME, Clauset A. Structure and inference in annotated networks. *Nat Commun*. 2016;7(1):11863.
51. Marsman M, Borsboom D, Kruis J, et al. An introduction to network psychometrics: relating using network models to item response theory models. *Multivariate Behav Res*. 2018;53(1):15–35.
52. Kuppens P, Sheeber LB, Yap MB, Whittle S, Simmons JG, Allen NB. Emotional inertia prospectively predicts the onset of depressive disorder in adolescence. *Emotion*. 2012;12(2):283–289.
53. Van de Leemput IA, Wichers M, Cramer, et al. Critical slowing down as early warning for the onset and termination of depression. *Proc Natl Acad Sci USA*. 2014;111(1): 87–92.
54. Lydon-Staley DM, Bassett DS. The promise and challenges of intensive longitudinal designs for imbalance models of adolescent substance use. *Front Psychol*. 2018;9(1):1576.
55. Forbes MK, Wright AG, Markon K, Krueger R. *On the Reliability and Replicability of Psychopathology Network Characteristics*. 2018. Retrieved from https://psyarxiv.com/re5vp/. Accessed May 21, 2018.