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Title: Symptoms of mood disorders in family carers of older people with dementia who experience caregiver burden: a network approach

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Ethics

The study was approved by the Research Ethics Committee of the Botucatu Medical School, São Paulo State University (UNESP) to protect the rights and welfare of humans participating in the research under CAAE permit no. 40558115.3.0000.5411. All participants agreed to participate spontaneously and signed an Informed Consent Term (CNS nº 466/2012 - Brazil).

Conflict of interest

All authors declare that they have no conflicts of interest.

Symptoms of mood disorders in family carers of older people with dementia who experience caregiver burden: a network approach

Abstract

Background: Informal carers of people with dementia are at greater risk of anxiety and depressive disorders if they find caregiving to be a burden. The aim of this study was to use a network analysis of cross-sectional data to investigate the relationships between anxiety and depressive symptoms in family carers of older people with dementia who experience burden.

Method: Sixty family carers exhibiting high levels of burden using the Zarit Burden Interview were included in the study. Participants completed the Hospital Anxiety and Depression Scale. The network analysis identified the depression and anxiety symptom network using features including a topological graph, network centrality metrics and communities analysis. The network was estimated through the graphical *LASSO* technique in combination with a *walktrap* algorithm to obtain the clusters within the network and the connections between the nodes (symptoms). A directed acyclic graph (DAG) was generated to model symptom interactions.

Results: The resulting network architecture shows important bridges between depression and anxiety symptoms. Lack of pleasure and loss of enjoyment were identified as potential gateway symptoms to other anxiety and depression symptoms and represent possible therapeutic targets for psychosocial interventions. Fear and loss of optimism were highly central symptoms, indicating their importance as warning signs of more generalized anxiety and depression.

Conclusions: This network analysis of depressive and anxiety symptoms in overburdened family carers provides important insights as to what symptoms may be the most important targets for behavioural interventions.

Key points

1. Lack of pleasure and loss of enjoyment were identified as being important gateways symptoms to more generalized anxiety and depression.

2. Fear and loss of optimism were shown to important in the propogation of anxiety and depression.

3. Each of these symptoms may associate with the social isolation, emotional and financial hardship associated with caring.

4. Psychosocial interventions for carers of people with dementia could be specifically targeted to mitigate against these symptoms.

<u>Introduction</u>

The number of people with dementia who require assistance for activities of daily living is rising, with a consequent rise in the number of informal caregivers for people with dementia (1). Caring for a person with dementia is associated with risks to the carer's mental health, resulting in higher rates of depressive syptoms, increased stress and reduced quality of life amongst carers (2). About 50% of informal carers of patients with dementia develop psychiatric symptomatology in the course of caregiving (3). These symptoms may be important if they either progress to formal psychiatric diagnoses such as anxiety and depression, or if they result in burnout, which renders carers unable to continue to provide support (4). The contribution of informal caregivers is socially and economically important (5) and understanding the pathways to psychiatric symptoms and burnout is critical if we are to develop a sustainable approach to care.

The association between stressful life events and the development of psychiatric symptoms is non-linear. Multiple studies which have considered these associations have failed to identify a single latent construct explaining their relationship (6,7). The causality is likely to be complex, rather than life events leading to a single diagnosis which, in turn, causes symptoms (8). If we are to understand how stressful life events experienced in the course of caring for people with dementia influence the development of psychiatric symptoms, a non-linear approach to analysis is therefore required. The network approach is one possible solution. It works on the basis that symptoms have an autonomous influence on one another and are therefore best represented as systems of causally-related mechanisms (9). Network analysis methods have been used to model a number of mental disorders and how they relate to life events, enabling them to be understood as complex systems (7,8,10–11). This exploratory study aimed to use network analysis to consider the relationships between symptoms of anxiety and depression in informal caregivers for people with dementia experiencing overload.

Methods

Participants

We aimed to describe how anxiety and depressive symptoms are associated in carers of people with dementia who are experiencing subjective caregiver burden. We conducted a cross-sectional study of carers of people living with dementia from the Geriatric Outpatient Clinic of the Botucatu Medical School, São Paulo State University (UNESP), Brazil. Between April 2015 and March 2017, all family carers of older people with a documented diagnosis of dementia in their medical records seen at the clinic were invited to take part. All carers ≥ 18 years with next-of-kin status were included. Carers identified by the research team as having cognitive impairment, based upon an initial screening with Mini Mental State Examination using the cut-offs

specified by Brucki et al(12), were excluded. Formal consent was undertaken prior to inclusion. All participants completed a Zarit Burden Interview (ZBI) and a Hospital Anxiety and Depression Scale (HADS). The ZBI (14) is a widely used measure of dementia caregiver burden and measures stress, subjective burden, perceptions, usual feelings and the impact of caring on caregivers' lives (15). A score of 21 or greater is regarded to be diagnostic of caregiver overload. The Brazilian version has 22 items with responses on a 5-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = quite frequently, 4 = nearly always) yielding a score of 0-88 points, where higher total score indicates greater burden (15). The HADS measures subjective symptoms of depression and anxiety using a 14-item self-completion questionnaire, with 7-items each considering anxiety (HADS-A) and depression (HADS-D). HADS has been validated in older populations up to 80 years of age(16). We chose it over other validated indices, such as the Geriatric Depression Scale (GDS) (17), because of its ability to describe symptoms of anxiety, which we thought might be important in carer response to dementia in addition to depressive symptoms. A validation study for a Brazilian version of HADS indicated that, for a cut-off score ≥8, the scale showed 93.7% sensitivity and 72.6% specificity for anxiety, and 84.6% sensitivity and 90.3% specificity for depression (18).

For participants identified as having overload using the ZBI cut-off of ≥ 21 points (19), we conducted a network analysis of their HADS responses. The aim of network analysis is to generate a graphical model which explains the interaction between psychometric variables. In this instance we sought to build a model where: HADS questionnaire items were represented by "nodes"; the relationship between questionnaire items were represented by lines, called "edges" in network analysis terminology; the weight of the lines representing edges demonstrated the strength of

association between questionnaire items; and where strongly associated items were grouped as clusters.

Estimating a network structure

To build our network we used a graphical LASSO (Least Absolute Shrinkage and Selection Operator) model (19). The LASSO adaptive method constrains the network to present only the most relevant connections to the data structure. This algorithm causes smaller correlations to be reduced to zero, resulting in a parsimonious network. For this type of network, findings are easiest to interpret when presented visually. To do this, the positive edges were drawn so that the stronger a connection, the thicker and more saturated it was. We set the maximum edge value to 0.46, the strongest edge identified in the network. The closer to this value, the stronger, thicker and more saturated the connection was. Symptoms with thick and highly saturated lines on visual inspection were regarded as being highly linked.

We calculated centrality metrics for each of the nodes. These describe the degree to which a particular node is important to the rest of the network (20). Node strength, betweenness, and closeness were all calculated. Node strength is the sum of all the weights connected to a given node, betweenness is the number of times that a node lies on the shortest path between two other nodes, and closeness is the average length of the shortest path between the given node and all other nodes in the network.

As a final step, we used a Directed Acyclic Graph (DAG) to consider the possible causal directions of the relationships between nodes. DAG is a Bayesian network approach that gives information about both the strength and the direction of connections. This was well explained by Moffa et al (21): "Take a simple example in which A and B both have to precede C. In cross-sectional data we might then observe: only

A; only B; A and B; A, B and C; or none. In contrast if there is no relationship between A, B and C, then any possible combination could be observed." DAG provides a means to separate participants at different steps of this causal progression, thus enabling the direction of causality to be inferred. Each DAG has a topological ordering that provides preliminary hints as to which symptoms may play a causal role in creating other symptoms, with causal symptoms situated at the top of the DAG.

Results

Ninety-six individuals were invited to participate, 6 of whom refused. Ninety participants underwent ZBI, 60 of whom had a score $\geq$ 21 indicating carer overload. There were 5 males and 55 females, with a mean (range) age of 57.48 (32-74) years. Thirty-four participants were married, 13 divorced and 13 single. Kinship was son or daughter (n = 42), wife or husband (n = 6), grandson or grandaughter (n = 5), daughter in law (n = 3), sister (n = 1), niece (n = 1) and close friend (n = 2).

Regularized Partial Correlation Networks

The goal here was, using LASSO, to obtain a network structure in which as few connections as possible were required to parsimoniously explain the covariance among variables in the data. Figure 1 shows the resulting network.
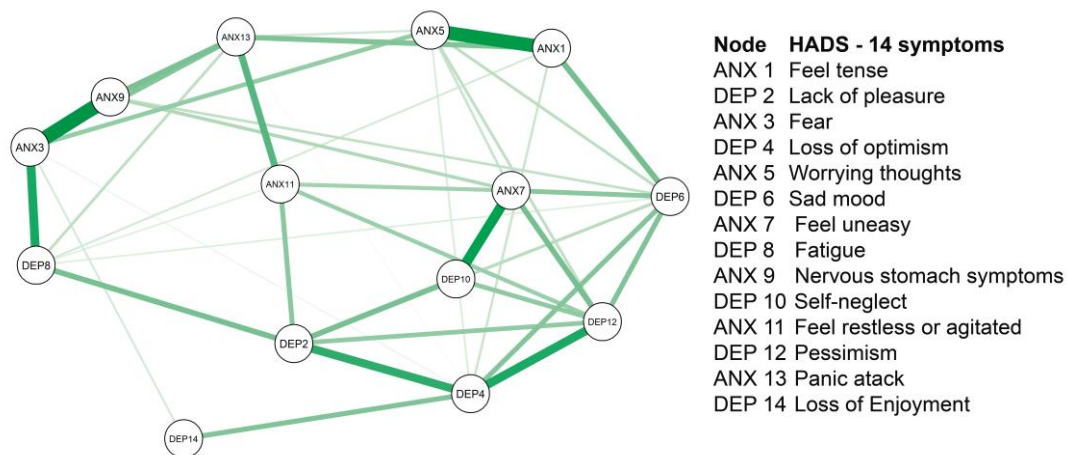
Figure 1 Graphical LASSO model of anxiety and depression symptoms in 60 caregivers. Nodes represent symptoms of anxiety (ANX) or depression (DEP), and edges represent regularized partial correlations between symptoms. Thicker edges represent stronger correlations.

Important bridges between depression and anxiety symptoms emerged. The depressive symptom *Sad mood,* together with the anxiety symptom *Feel tense,* was highly linked to the anxiety symptom *Worrying thoughts.* The anxiety symptom *Panic attack*, together with the anxiety symptoms *Nervous stomach symptoms* and *Fear,* linked to the depressive symptom *Fatigue.*

The importance of nodes in a network are expressed using measures called centrality índices. Node centrality metrics of the graphical LASSO are presented in Figure 2. In this, items with less centrality have negative values and items with more centrality have positive values. In psychopathology networks, a node with a high index of centrality is important in the flow of information or the propagation of symptoms in the network. The higher the index of centrality the more central the node is in the network, meaning it has links to many other symptoms in the network (22). *Lack of pleasure* and *loss of optimism* emerged as the most central nodes in the network for betweenness, which indicates that these two symptoms often appeared on the shortest path between two other symptoms. Nodes high in betweenness are important for transmitting information

through the network (23). *Lack of pleasure, loss of optimism* and *pessimism* had high

centrality for closeness, indicating that they are nodes that are more likely to quickly
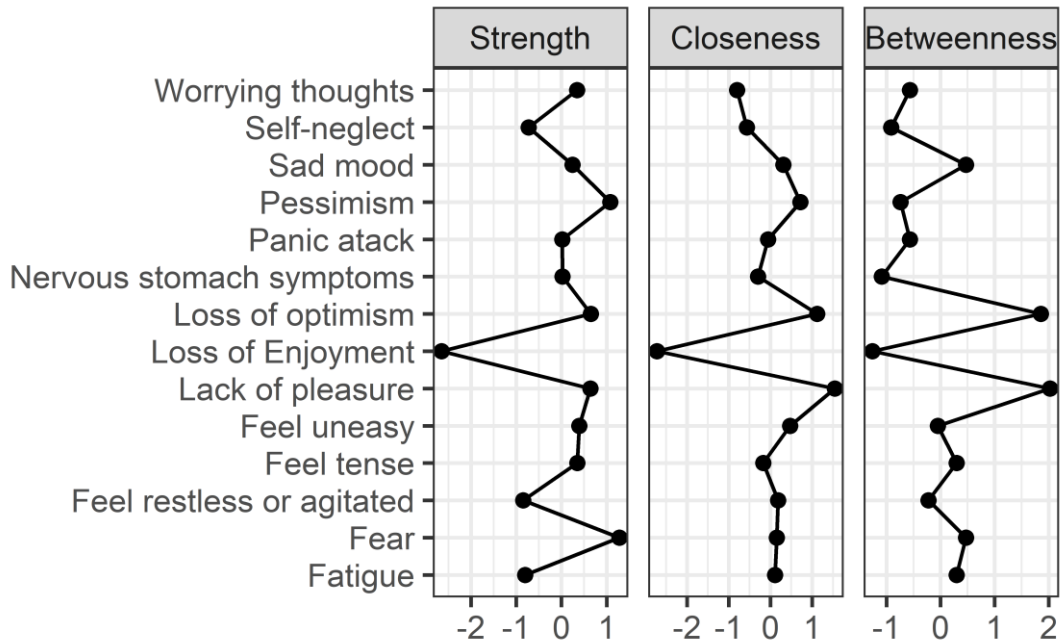
affect other symptoms (24).

Figure 2 Centrality plot for the Graphical LASSO using standardized measures of node strength, closeness and betweenness.

Bayesian directed network (Directed acyclic graph; DAG)

Directed Acyclic Graphs (DAGs) are Bayesian networks whereby nodes are connected

by arrows (called directed edges). A directed edge from one node to another represents

a relationship between those two nodes (25,26). DAGs have a topological ordering that

shows upstream and downstream variables with the direction allowing causation to be

inferred. In this study, DAG was used to generate rather than test hypotheses because it

is difficult to establish temporal precedence from cross-sectional data. Using DAG with

cross-sectional data can help determine what to investigate in future time-series or

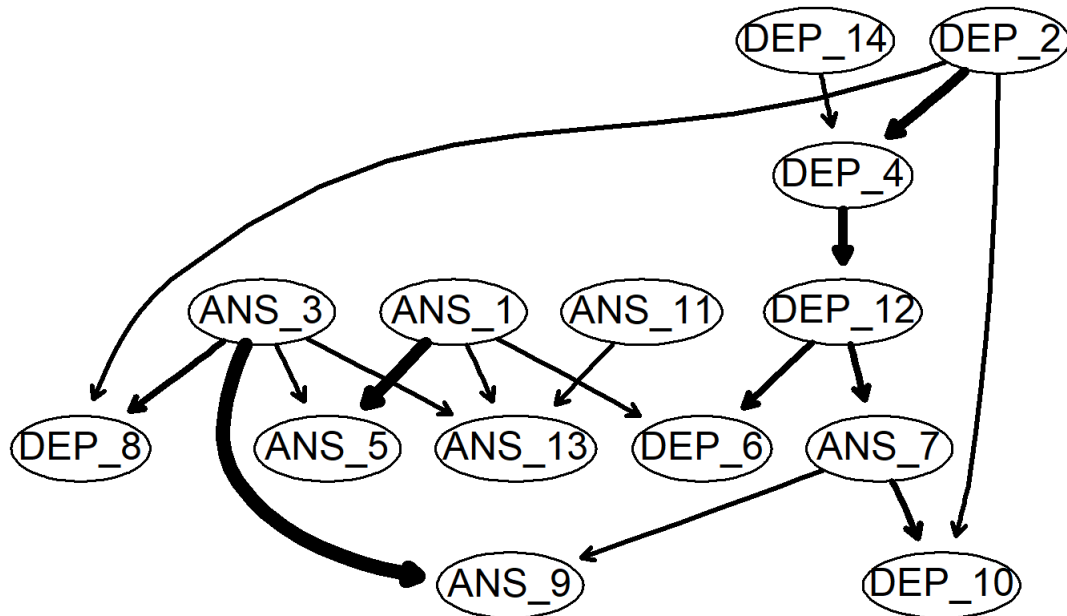experimental procedures. Figure 3 shows the DAG generated in this study.

Figure 3 A Bayesian network (directed acyclic graph; DAG) depicting anxiety and depression symptoms in caregivers with overload. The graph shown is an average of 50,000 bootstrapped models.For details of the symptoms, see Figure. 1.

Symptoms at the top of the DAG are estimated to have greater predictive priority and are more salient (26). At the top of the DAG are the depressive symptoms *loss of enjoyment* and *lack of pleasure*. Liu et al (27) consider *lack of pleasure* as a cardinal feature of major depression. In our sample, this node activated three other nodes: *fatigue, self-neglect (loss of self-esteem) and loss of optimism*. Of these, *loss of optimism* had a high index of centrality, triggering the pessimism node. Three other independent nodes gave rise to several other symptoms of anxiety. *Fear* triggered *nervous stomach symptoms* and the *fatigue* node. *Feeling tense* triggered *worrying thoughts* (i.e rumination of negative thoughts), *panic* and *sad mood. Feel restless or agitated* also triggered *panic*.

Discussion

This paper investigated the dynamics of anxiety and depression symptoms in family caregivers who suffer overload when caring for older people with dementia. The main findings were: the importance of lack of pleasure and loss of enjoyment as initial

symptoms which trigger other anxiety and depression symptoms; the high level of centrality and betweenness of lack of pleasure in interactions between symptoms of both anxiety and depression; and the centrality of fear and loss of optimism to symptom networks.

Lack of pleasure showed both a high level of betweenness and a predominance in the dynamic acyclic graph, meaning that it was both a gateway symptom and linked to many other symptoms in the causal network. Lack of pleasure is an important part of diagnostic classifications for depression but its predominance here suggests that it may be both a predictor of more generalized symptoms of anxiety and depression and a logical target for intervention. In previous work, Boschloo et al (28) found a crucial role for the symptom of loss of interest and pleasure, and reported it to be the strongest predictor of receiving a diagnosis of major depression during the 6-year follow-up period in a sample of 501 adults. Lack of pleasure seems to act as the doorway to a cascade of depression symptoms: the feeling of being slower, loss of interest in personal appearance and depressed mood. Informal caregivers often have to deal with the prospect of greater social isolation, financial hardship, lack of leisure and time to care for themselves, permanent fatigue and worse health (29). Initiating practical steps to mitigate against these issues represents a potentially powerful approach to prevention of anxiety and depression.

The centrality of *fear* and *loss of optimism* is important because in a system of functional relationships, the activation of highly central symptoms increases the likelihood that the activation will spread to other symptoms because of the magnitude and number of connections. It is reasonable to hypothesize that strategies to avoid or treat fear and loss of enjoyment may promote a faster recovery. *Lack of pleasure*

showed high centrality indices and also appeared at the top of the directed graph. The *lack of pleasure* node, a loss of interest in generally pleasurable activities, appeared as a bridge between depressive symptoms, had a high index of closeness and betweenness, and lay on the shortest path between two other nodes. The corollary of these multiple observations is that *lack of pleasure* is an important symptom in the maintenance of depression and anxiety and may be a further important therapeutic target.

There are several clinical implications of the current findings. As mentioned, the LASSO networks provide us with a view of how symptoms are interrelated with greater clarity. First of all, we believe that network approaches to cross-sectional data can yield some useful preliminary causal data. This, in turn, can direct future experimental studies which remain the gold standard for establishing causality. The present study identified highly central symptoms that may represent the primary targets of therapeutic intervention. The DAG analysis suggests that targeting the symptom of *lack of pleasure* earlier could improve the efficacy of psychosocial interventions. As lack of time in leisure activities was located at the top of the DAG and therefore was estimated to have greater priority, this symptom could be a target for early intervention to eliminate or truncate the progress of anxiety and depression as part of caregiver burden. These findings offer greater clarity for health and social care professionals as to the important and central symptoms for caregivers of people with dementia when faced with overload. Greater understanding of these symptoms may allow for improved identification of, and appropriately staged interventions for, emerging anxiety and depression in caregivers of people with dementia. A previous systematic review of reviews (30) found that multicomponent interventions to maintain the psychological health of carers could improve carer wellbeing, burden and self-efficacy. Interventions were more likely to be effective if they included an educational component, focused on enhancing carers'

knowledge, as well as a therapeutic component such as cognitive behavioural therapy. Importantly, that review did not establish the optimal sequencing or configuration of components in a multi-component intervention. Research, of the type presented here, that enables a better understanding of the pathway to symptoms of anxiety and depression in carers for people with dementia provides the basis for further work to help configure these multicomponent interventions in an evidence-based way.

The strengths of this study lie in the carefully collected data from a cohort of clinical patients and in the ability of network analysis to propose causal associations between symptoms of anxiety and depression. There were two main limitations. First, our sample size was relatively small considering the high statistical power necessary in network analysis. A consequence is that estimated parameters were associated with wide confidence intervals. Second, the edges were calculated with cross-sectional data, making estimations of some network characteristics more tentative. Although approaches such as the graphical LASSO and DAG can move cross-sectional data closer to a causal interpretation, experimental and prospective designs are required to test the hypotheses generated. The importance of this work is in suggesting possible targets – lack of pleasure, fear and loss of optimism – which could be amenable to non-pharmacological interventions. Further research should focus on these domains.

Ethical Approval

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