UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO

TESE DE DOUTORADO

Religiosidade, Espiritualidade, Desfechos Clínicos e Marcadores Biológicos na Depressão

Bruno Paz Mosqueiro

Orientador: Marcelo Pio de Almeida Fleck

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"Truly, it is in the darkness that one finds this light, so when we are in sorrow and distress, then this light is nearest of all to us"
(Eckhart, 1327)

"I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me".
(Isaac Newton, 1643-1747)

SUMÁRIO

ABREVIATURAS E SIGLAS

TDM - transtorno depressivo maior.

BDNF - fator neurotrófico derivado do cérebro (*brain-derived neurotrophic factor*).

R/E – religiosidade/espiritualidade.

OR - religiosidade organizacional (*organizational religiosity)*.

NOR - religiosidade não-organizacional *(non-organizational religiosity)*.

RI – religiosidade Intrínseca.

HIR – religiosidade intrínseca alta (*high intrinsic religiosity*).

LIR – religiosidade intrínseca baixa (*low intrinsic religiosity)*.

DUREL – Escala de Religiosidade da Universidade de Duke (*Duke University Religion Index).*

ER – Escala de Resiliência (*Resilience Scale*).

RS – Resilience Scale.

HAM-D – escala de depressão de Hamilton (*Hamilton Depression Rating Scale).*

MSM - método de estadiamento de depressão Maudsley (*Maudsley Staging Method*).

CGI – Escala Impressão Clínica Global (*Clinical Global Impression Scale).*

CIRS - Índice de Comorbidades Clínicas (*Cumulative Illness Rating Scale*).

BPRS – Escala Breve de Avaliação Psiquiátrica (*Brief Psychiatry Rating Scale).*

WHOQOL-SRPB – escala para avaliação da religiosidade, espiritualidade, crenças pessoais e qualidade de vida da Organização Mundial de Saúde, versão abreviada (*World Health Organization Quality of Life Religiousness, Spirituality and Personal Beliefs instrument).*

MOS – Escala de Suporte Social MOS (*Medical Outcomes Study's Social Support Scale*).

mgm - software ligado a análise estatística de redes através da linguagem e plataforma R (*Mixed Graphical Models).*

RESUMO

A depressão representa um transtorno mental de grande prevalência e impacto para saúde pública. Pacientes com quadros depressivos em atendimento terciário apresentam em geral quadros com sintomatologia mais grave, com maior recorrência, menor chance de remissão dos sintomas e maior risco de suicídio. Sendo assim, o entendimento de fatores capazes de melhorar o prognóstico e tratamentos, em especial nos pacientes com maior gravidade e riscos, constitui importante questão de pesquisa para psiquiatria e saúde mental.

A religiosidade e espiritualidade (R/E), por sua vez, têm sido consideradas como importantes fatores na avaliação e tratamento de pacientes com depressão. No Brasil, por exemplo, boa parte dos pacientes consideram a religiosidade como algo muito importante em suas vidas e muitos pacientes desejam abordar tais fatores em seus atendimentos de saúde. Evidências científicas reforçam que em geral pacientes com maior R/E possuem menor risco de suicídio, maior recuperação de sintomas depressivos e menor incidência de depressão em estudos prospectivos. Por outro lado, o entendimento dos mecanismos através dos quais a R/E exerce seus efeitos sobre desfechos clínicos na depressão segue como relevante fator a ser compreendido pela pesquisa em saúde mental.

O objetivo da presente tese é avaliar em pacientes com depressão atendidos na internação e ambulatório do Hospital de Clínicas de Porto Alegre a relevância e impacto da R/E na depressão sobre diferentes perspectivas: (1) avaliação da percepção e importância do tema pelos pacientes; (2) entendimento das relações entre diversas dimensões da R/E, fatores positivos (e.g. resiliência, suporte social) e sintomas depressivos; (3) impacto da R/E no risco de suicídio e remissão de sintomas depressivos em 6 meses de tratamento; e (4) correlação da R/E com marcadores biológicos em pacientes com depressão internados.

Os resultados apresentados nos estudos demonstram que a maior parte dos pacientes apresenta interesse sobre religiosidade e espiritualidade (82,1%), embora a maioria (63,1%) nunca tenha sido questionados em seus atendimentos de saúde sobre o tema. Além do mais, 68.3% dos pacientes gostariam de participar em uma psicoterapia integrada a espiritualidade no seu tratamento para depressão. Fatores positivos como resiliência, propósito, esperança, fé, foram identificados como possíveis mediadores de efeitos positivos da R/E em análise de rede de pacientes com depressão. Em seguimento prospectivo de 6 meses, uma maior frequência a encontros religiosos (DUREL) foi relacionado a chances 80% maiores de remissão de sintomas depressivos (OR 1.83, P=0.02). Diversas dimensões da R/E, por sua vez, como religiosidade intrínseca (DUREL) (t-statistic -2.421, P=0.01), frequência a encontros religiosos (DUREL) (t-statistic -2.172, P=0.03) e escore total de qualidade de vida ligada a religiosidade, espiritualidade e crenças pessoais (WHOQOL-SRPB) (t-statistic -3.670, P=0.00) demonstraram correlações negativas com risco

de suicídio. Ademais, em pacientes com depressão internados, efeitos positivos e protetores da religiosidade intrínseca foram correlacionados a maiores níveis do fator neurotrófico derivado do cérebro (BDNF, *brain-derived neurotrophic factor*) na alta hospitalar, possível marcador de neuroplasticidade cerebral e mediador dos efeitos da R/E sobre depressão.

Os resultados apresentados reforçam a relevância do estudo da R/E na psiquiatria, apresentam possíveis mediadores de efeito da R/E sobre a depressão e salientam a importância clínica de sua abordagem em pacientes com sintomatologia grave de depressão.

ABSTRACT

Depression represents a common disorder with a relevant impact on public health. Depressed patients in specialized tertiary care, usually present worse clinical outcomes, including higher recurrence of depressive episodes, lower remission rates, and higher suicide risk, compared to community depressed patients. Considering that, understanding factors capable to improve treatment and prognosis, especially for those patients with worse symptomatology, certainly represents a key issue to psychiatry and mental health research.

Religiosity and spirituality, otherwise, are increasingly recognized as relevant aspects to be addressed among depressed patients. In Brazil, particularly, most individuals consider religiosity and spirituality (R/S) a very important aspect of their lives, and most patients would like to address those issues in their health consultations. Empirical evidence, reinforces that, generally, patients with more R/S present lower suicide risk, higher improvement of depressive symptoms and lower incidence of depressive episodes in prospective studies. Nevertheless, undertanding the pathways toward which R/S exert their effects in depression remains a key issue to mental health research.

The present thesis aimed to evaluate in samples of tertiary care depressed patients at psychiatric inpatient unit and outpatient mood disorder clinic, the role of R/S over depressive disorder from different perspectives: (1) perception of relevance and patients interest in R/S issues; (2) evaluate the complex interplay between different R/S domains, positive mental health factors (e.g. resilience, social support) and depressive symptoms; (3) the impact of R/S over suicide risk and 6-month prospective remission rates of depressive symptoms; and (4) the relationship between R/S and biological markers of depressive disorders among depressive inpatients.

Our findings showed that most patients identify that R/S represent a significant aspect of their health care (82.1%), but most of them were never asked about those topics in health care consultations (63.1%). Furthermore, 68.3% of patients demonstrate interest in spiritually integrated psychotherapy in their treatment of depression. Positive health factors such as resilience, hope, purpose, faith, but not social support, were identified as potential pathways across R/S and better outcomes of depressive symptoms in a network analysis. In a 6-month prospective follow-up, religious attendance (DUREL) was identified as a key predictor of remission of depressive symptoms, with 80% higher odds of remission in the follow-up in patients with higher religious attendance (OR 1.83, P=0.02). Different R/S domains, including religious attendance (DUREL) (t-statistic -2.172, P=0.03), intrinsic religiosity (DUREL) (t-statistic -2.421, P=0.01) and religiousness, spirituality and personal beliefs quality of life (WHOQOL-SRPB) (t-statistic -3.670, P=0.00), were inversely related to

suicide risk. Moreover, in a sample of depressive inpatients, higher intrinsic religiosity was correlated to higher BDNF serum levels at discharge, a potential biological marker of recovery and neuroplasticity in depressed patients.

The present findings reinforce the relevance of R/S and psychiatric research and the importance to address those issues in clinical practice. The findings also revealed potential mechanisms or pathways to understand the benefits of R/S over depression, especially among those patients with more severe depressive symptoms and higher risks.

1. APRESENTAÇÃO

O trabalho desenvolvido na presente tese de doutorado denominada "Religiosidade, Espiritualidade, Desfechos Clínicos e Marcadores Biológicos na Depressão" tem origem no interesse em compreender a relação entre religiosidade e espiritualidade (R/E) e depressão em diferentes níveis: a associação entre R/E e resposta ao tratamento, a sua possível influência em desfechos clínicos e marcadores biológicos, a busca de entendimento de possíveis mediadores de efeito da R/E na depressão, bem como a percepção dos pacientes deprimidos sobre a importância do tema.

A tese inicia com a apresentação da base conceitual e um panorama de pesquisas e evidências científicas na área de R/E e saúde mental. A seguir é apresentada uma breve revisão sobre o impacto da R/E na depressão e os diferentes desenhos de pesquisa desenvolvidos para avançar no entendimento do tema. Após são descritos os objetivos, hipóteses, considerações éticas e apresentação dos artigos que compõem a tese.

Ao final são discutidas perspectivas futuras e conclusões, incluindo oportunidades para pesquisas e desafios para abordagem do tema na prática clínica. Em anexo, além de documentos relevantes relacionados a tese e artigos, são apresentados relatos de atividades de divulgação científica e publicações complementares ligadas ao tema desenvolvidas ao longo do período de desenvolvimento do projeto. A presente tese resultou em 4 artigos como primeiro autor, 4 artigos como autor participante, 1 resumo apresentado em conferência internacional, 3 capítulos de livro acadêmicos internacionais e participação como editor de livro internacional sobre saúde mental e espiritualidade. O autor apresentou seu trabalho nas seguintes atividades: Ciclo de Avanços em Psiquiatria da Associação de Psiquiatria do Rio Grande do Sul (APRS), Jornada de Psiquiatria do Centro de Estudos Luís Guedes (CELG-UFRGS), Congresso Brasileiro de Psiquiatria (ABP), Congresso Mundial de Psiquiatria (WPA) e Encontro Mundial de Psiquiatria e Espiritualidade da Organização Mundial de Psiquiatria (WPA).

2. BASE CONCEITUAL E REVISÃO DA LITERATURA

2.1. Depressão

2.1.1.Epidemiologia, Diagnóstico e Tratamento

A depressão constitui transtorno mental de grande prevalência e impacto para saúde pública mundial (Liu et al., 2019). Estudos epidemiológicos identificam uma prevalência de depressão em média de 5% da população mundial nos últimos 12 meses e entre 15 a 18% ao longo da vida (Kessler & Bromet, 2013). Revisão sistemática de estudos estima prevalência média de depressão no Brasil de 8% nos últimos 12 meses e em torno de 17% ao longo da vida, com variações de acordo com critérios e mensurações utilizados (Silva et al., 2014).

Por sua condição crônica, grave ou recorrente, a presença de sintomas depressivos ao longo da vida representa fonte de sofrimento psíquico, prejuízos interpessoais e na qualidade de vida de muitas pessoas (Cho et al., 2019). O estudo *Global Burden of Disease*, por exemplo, estima que a depressão contribui como a terceira principal causa de disfuncionalidade no mundo (em inglês Disability Adjusted Life Years ou DALYs[1]), e diante do envelhecimento da população e mudanças globais possui perspectivas de se tornar a principal causa de disfuncionalidade até o ano de 2030 (Liu et al., 2019).

O diagnóstico de transtorno depressivo maior (TDM) é realizado a partir de entrevista clínica para caracterização de sintomas, tempo de duração e prejuízos funcionais do indivíduo, utilizando como critérios diagnósticos os sistemas classificatórios como CID-10 e DSM-V (Malhi & Mann, 2018). O diagnóstico do episódio depressivo é identificado por sintomas persistentes (diários ao longo de no mínimo 2 semanas) que incluem tristeza, desânimo ou perda de prazer, associados à diminuição de energia, cansaço, alterações de apetite, do sono e libido, alterações psicomotoras (lentificação ou agitação), dificuldades de concentração e sintomas cognitivos e emocionais que incluem culpa, ideias de desvalia, e por vezes pensamentos de morte, ideação, planos e tentativas de suicídio (DSM-5, 2013).

[1] Disability Adjusted Life Years (DALYs): medida que permite calcular o impacto ou carga (*burden*) associada a uma doença ou transtorno em uma população. A medida DALYs (anos de vida perdidos ajustados por incapacidade), é resultante da soma dos anos perdidos por morte prematura (*YLL ouyears of life lost*) e anos perdidos por incapacidade (*YLD ou years lived with disability*) (Murray et al., 2012).

Os antidepressivos representam tratamento de primeira linha e com comprovada eficácia para tratamento da depressão (Cipriani et al., 2018). Abordagens psicoterápicas com evidências científicas (e.g. terapia cognitivo-comportamental e psicoterapia interpessoal), outros psicofármacos adjuvantes, terapias somáticas, eletroconvulsoterapia e exercícios físicos representam estratégias de tratamento adicionais recomendadas com benefícios para muitos pacientes (Cuijpers et al., 2016; Malhi & Mann, 2018; Schuch et al., 2018).

Entretanto, mesmo com tratamentos vigentes, estudos identificam que ao menos 10 a 20% dos pacientes não apresentam remissão de sintomas após diversas abordagens terapêuticas (Gaynes et al., 2009). Conforme atestam evidências de diversos estudos prospectivos, quanto maior a gravidade, duração do episódio e quantidade de episódios depressivos, menores são a chances de resposta aos tratamentos e recuperação (Keller, 1992). Estudo recente em pacientes ambulatoriais na Holanda, por exemplo, relata que em 6 anos 55% dos pacientes apresentavam sintomas depressivos ou ansiosos persistentes e apenas 17% dos pacientes apresentavam melhora completa dos sintomas, sugerindo que a remissão dos sintomas pode ser mais incomum do que esperado por estudos anteriores (Verduijn et al., 2017). Em amostras de pacientes mais graves e com depressão refratária ao tratamento, as taxas de remissão dos sintomas depressivos variam de 3,6% a 50% em 12 meses de seguimento, de acordo com a gravidade e refratariedade dos sintomas nas populações estudadas (Dunner et al., 2006; Keller, 1992).

2.1.2. Suicídio e Depressão

O suicídio representa uma das maiores complicações ligadas aos quadros depressivos (Fazel & Runeson, 2020). Conforme dados apresentados pela Organização Mundial da Saúde ao redor de 800 mil pessoas no mundo cometem suicídio anualmente (Bachmann, 2018). No Brasil dados relatam uma incidência de 5,5 casos de suicídio para cada 100.000 habitantes, demonstrando tendência geral de crescimento nas últimas duas décadas (Rodrigues et al., 2019). Em casos de depressão grave, crônicos ou refratários, comumente atendidos em centros de referência especializados, situações de risco de suicídio se tornam ainda mais prevalentes (Dong et al., 2019; Mosqueiro et al., 2015).

Modelos de compreensão do risco de suicídio vigentes identificam fatores de risco para o suicídio a nível individual e populacional. Entre os fatores de risco individuais os transtornos psiquiátricos (depressão, transtorno bipolar, psicoses, transtornos por uso de substâncias) possuem tamanho de efeito maior, além de histórico de tentativas de suicídio prévias, traumas na infância, história familiar de suicídio (particularmente perda de um dos pais por suicídio nos primeiros anos da infância), traços de personalidade com maior

impulsividade ou neuroticismo, e privações econômicas ou financeiras significativas (Fazel & Runeson, 2020).

Além dos fatores de risco, tentativas de suicídio podem ser desencadeadas por fatores precipitantes como uso abusivo de álcool ou drogas, acesso a meios letais, estressores e adversidades, diagnóstico de doenças graves e relatos de suicídio apresentados na mídia. Os fatores precipitantes possuem impacto diverso para cada indivíduo em diferentes momentos da vida, de acordo com fatores de risco individuais e populacionais pré-existentes, tornando modelos preditivos e explanatórios ao risco de suicídio complexos (Fazel & Runeson, 2020).

Embora o conhecimento dos principais fatores de risco e precipitantes ao suicídio, programas de prevenção baseados na identificação e tratamento dos indivíduos em risco não tem alcançado efeito adicional esperado na diminuição da incidência do suicídio em muitos países, como Estados Unidos (Chen & VanderWeele, 2020). Políticas de restrição ao uso de álcool e diminuição no acesso a meios potencialmente letais, por exemplo, (e.g. redução da eliminação de monóxido de carbono no gás de uso domiciliar, políticas de controle a pesticidas e restrição ao acesso a armas de fogo), são fatores que parecem contribuir para diminuição da incidência de casos de suicídio em estudos populacionais (Fazel & Runeson, 2020).

Além da abordagem dos indivíduos em risco, estratégias com foco também na promoção de fatores de proteção ao suicídio tem sido propostas para todos os níveis de prevenção (primordial a terciária), incluindo a religiosidade e espiritualidade como fatores individuais e comunitários com potencial impacto positivo na prevenção ao suicídio (Chen & VanderWeele, 2020; Lawrence et al., 2016).

2.1.3. Fisiopatologia e Marcadores Biológicos na Depressão

Com os avanços na pesquisa e epidemiologia psiquiátricas diversos fatores de risco e correlatos neurobiológicos para depressão tem sido descritos na literatura científica (Seo et al., 2017). Entretanto, não existe modelo fisiopatológico único capaz de explicar e predizer as alterações existentes nos diversos pacientes e quadros depressivos.

Diversos marcadores biológicos e hipóteses neurobiológicas têm sido descritos e estudados ao longo das últimas décadas, desde o surgimento das teorias monoaminérgicas a partir das evidências de eficácia de antidepressivos tricíclicos e inibidores da MAO na metade do século XX, seguindo-se com o estudo de alterações no eixo hipotálamo-hipófise-adrenal e cortisol, e teorias mais recentes sobre alterações em citocinas inflamatórias,

neuroplasticidade, epigenética e conectividade cerebral em estudos de neuroimagem funcional (Kowianski et al., 2018; Malhi & Mann, 2018).

Considerando que a história familiar representa 39% da herdabilidade da depressão, fatores genéticos também se mostram relevantes para compreensão da fisiopatologia depressão (Kendler et al., 2001). Nesse sentido, os estudos de associação em varreduras genômicas (*genome wide association studies* ou GWAS), contribuem na identificação de possíveis áreas do genoma relacionadas a depressão. Metanálise recente incluindo 3 estudos de GWAS (n= 807.553), por exemplo, identificou mais de 102 áreas do genoma para exploração em estudos futuros, com destaques para áreas do córtex pré-frontal, presença de áreas do genoma comuns em outros diagnósticos psiquiátricos (e.g. esquizofrenia, TDAH, neuroticismo), além de outros achados mais gerais ligados ao metabolismo e absorção de medicamentos (Howard et al., 2019; Ormel et al., 2019). Estudos de epigenética, por sua vez, contribuem para compreensão mais detalhada das interações entre gene-ambiente, utilizando por vezes hipóteses provenientes de estudos como GWAS, e são capazes de promover maior entendimento da vulnerabilidade e fisiopatologia da depressão (Caspi et al., 2003; Pena & Nestler, 2018).

2.1.4. BDNF e Neuroplasticidade Cerebral

O fator neurotrófico derivado do cérebro (*brain-derived neurotrophic factor ou BDNF*) é uma das neurotrofinas cerebrais mais relevantes e extensivamente estudadas desde sua descoberta em 1989 por Yves-Alain Barde (professor de neurobiologia da Universidade de Cardiff e Instituto Max Planck) e Hans Thoenen (Instituto Max Planck de Psiquiatria e posteriormente Neurobiologia) (Kowianski et al., 2018).

O BDNF possui papel relevante na plasticidade sináptica, formação dendrítica e na sobrevivência neuronal (Kowianski et al., 2018). Estudos indicam que também exerce efeitos moduladores na substância cinzenta em diferentes regiões do córtex pré-frontal e hipocampo, apresentando relevante papel na memória e cognição (Na et al., 2016). Nas últimas 2 décadas tem sido estudado como potencial marcador de neuroplasticidade cerebral em pacientes com depressão (Polyakova et al., 2015) e neuroprogressão em pacientes com transtornos mentais graves (Kapczinski et al., 2017).

Metanálises identificam que existe consistente diminuição dos níveis de BDNF séricos em pacientes com depressão comparados a controles saudáveis e um significativo aumento nos níveis de BDNF em pacientes que apresentam resposta a antidepressivos e melhora nos sintomas depressivos, reforçando um relevante papel do BDNF como marcador biológico periférico na depressão (Kishi et al., 2017; Molendijk et al., 2014).

A heterogeneidade clínica da depressão e diagnóstico psiquiátrico e a multiplicidade da efeitos e interações complexas com outros fatores em diferentes áreas cerebrais são potenciais fatores que limitam a aplicabilidade clínica de marcadores biológicos como BDNF e um entendimento mais específico de seu papel na fisiopatologia da depressão (Hosang et al., 2014; Peterson et al., 2018).

2.1.5.Novos Modelos e Análises de Rede na Depressão

A heterogeneidade da depressão, com diversos fatores de vulnerabilidade e marcadores biológicos, pode ser considerado um dos principais motivos que limitam a compreensão mais específica da depressão e sua fisiopatologia (Beijers et al., 2019). Apesar dos avanços, os dados existentes ainda não permitem a generalização e aplicabilidade clínica dos achados de pesquisas.

Nesse sentido, diversas abordagens metodológicas recentes tem procurado novas formas de avaliação e questionado modelos existentes tradicionais de psicopatologia da depressão (Kendler, 2016). O projeto iniciado em 2009 pelo NIMH "*Research Domain Criteria",* por exemplo, tem como objetivo estimular pesquisas para identificar subtipos diagnósticos na psiquiatria a partir de dados neurobiológicos e comportamentais mais objetivos e independentes dos sistemas classificatórios atuais como DSM ou CID (Cuthbert & Insel, 2010). Outras abordagens, como análises estatísticas com classes latentes, a partir da avaliação de subgrupos mais homogêneos dentro de populações maiores de pacientes, tem procurado aprimorar a validade e especificidade clínica no estudo da depressão e correlação com desfechos clínicos (Li et al., 2014). Ademais, modelos estatísticos com capacidade de análise de grande número de dados (*Big Data*) e modelos de inteligência computacional (*Machine Learning)* também tem sido utilizados para melhorar a capacidade de predição, prognóstico e exploração de dados, permitindo novos insights na avaliação dos quadros depressivos (Beam & Kohane, 2018; Gradus et al., 2019; Islam et al., 2018).

As análises de rede (*Network Analysis*) representam metodologia de análise aplicada recentemente na psiquiatria e depressão, embora sua utilização a mais tempo em estudos de biologia e ciências sociais (Haslbeck & Waldorp, 2019). Tem como princípio a hipótese de que a depressão não poderia ser considerada uma entidade única, com sintomas e quadros clínicos definidos e homogêneos, a exemplo dos sintomas e alterações esperadas em outras doenças clínicas resultantes de uma causa comum (e.g. alterações respiratórias e em exames resultantes da infecção pelo bacilo da tuberculose) (Cramer et al., 2016). O episódio depressivo seria melhor entendido a partir da interação complexa de diversos sintomas, em combinações e com efeitos diferentes, que dariam origem a síndrome depressiva (Beard et al., 2016). Por exemplo, alguns pacientes podem ter como sintomas centrais na origem do episódio depressivo a perda de sono, que desencadearia cansaço,

dificuldades cognitivas, dificuldades laborais e por fim episódio depressivo completo. Para outros pacientes, os sintomas centrais podem ser ansiedade, irritabilidade, culpa, desvalia ou anedonia, que em combinações diversas podem dar origem ao mesmo síndrome depressiva.

Entre seus objetivos as análises de rede permitem: (1) uma representação visual da interação entre sintomas, características ou variáveis estudados; (2) o entendimento de quais variáveis apresentam um papel central na rede ou grupo de variáveis em análise (*centrality measures)*; (3) análise exploratória (*data driven)* e identificação de mediadores de efeito e interações complexas entre variáveis, controladas estatisticamente pelo efeito umas das outras e (4) a predição de desfechos clínicos a partir da conectividade das redes estudadas em comparação com outras redes (Chang et al., 2019).

Estudos recentes identificam que pacientes com depressão possuem diferentes conexões (*edges*) entre sintomas depressivos e cada sintoma ou variável *(nodes)* apresenta centralidade e relevância diferente na rede como um todo (ver figura 1) (Van Borkulo et al., 2015). A força geral das conexões entre os sintomas em análise de rede de pacientes com depressão tem sido capaz de predizer o prognóstico e chances de melhora em estudos prospectivos (McElroy et al., 2019; Van Borkulo et al., 2015).

Considerando a complexidade dos sintomas depressivos e sua relação com variáveis multidimensionais, como religiosidade e espiritualidade, as análises de rede podem contribuir para melhor entendimento das relações entre esses fatores.

2.1.5.Fatores Positivos e Promoção de Saúde Mental

Um dos caminhos para compreender desfechos significativos em saúde tem sido o uso de avaliações baseadas na percepção dos pacientes (*patient-reported outcomes*). Desfechos como bem-estar, qualidade de vida, e aspectos pessoais e culturais tem sido relacionados como desfechos importantes em saúde a partir da percepção dos pacientes (Cloninger, 2006; Panzini et al., 2017; Vares et al, 2015).

Na saúde mental em geral, e na medicina particularmente, existe conhecimento muito maior sobre de fatores preditores e agravantes de doenças e transtornos mentais do que de fatores e processos positivos que promovem crescimento, saúde, prevenção do adoecimento e desenvolvimento dos indivíduos (Ungar & Theron, 2020; VanderWeele et al., 2019). Nesse contexto, comportamentos e atitudes positivas (e.g. resiliência, gratidão, esperança, otimismo) tem sido recentemente estudados por suas relações protetoras e relevantes em saúde mental e psiquiatria (Jeste et al., 2015; Vaillant, 2013).

De grande interesse para área de saúde mental, especialmente na depressão e suicídio, são os estudos sobre propósito ou sentido existencial. Viktor Frankl, psiquiatra e psicanalista Vienense, a partir da própria experiência de sobrevivência a campos de concentração nazistas, destaca a relevância do sentido existencial como condição norteadora para vida e superação das adversidades. Frankl destaca as relações da religiosidade como uma forma de "supra-sentido" existencial, constituindo força de segurança, resiliência e autotranscendência (Silveira & Mahfoud, 2008). Evidências recentes identificam que pessoas que possuem um claro propósito de vida apresentam efeitos protetores para saúde, incluindo resultados significativos para saúde e menor mortalidade por doenças em geral (Alimujiang et al., 2019; VanderWeele et al., 2019).

Particularmente na depressão, diversos estudos identificam um papel protetor para saúde mental da presença e percepção de maior suporte social pelos indivíduos (Leskela et al., 2006; Van den Brink et al., 2018). Nesse sentido, intervenções psicoterápicas (Psicoterapia Interpessoal ou TIP) com foco na ampliação e qualidade das relações e procura de suporte social, reconhecidamente apresentam eficácia no tratamento e prevenção da depressão (Cuijpers et al., 2016).

Outras iniciativas como o Projeto WHOQOL da Organização Mundial da Saúde tem procurado estudar fatores relacionados a qualidade de vida como importante desfecho a ser avaliado em saúde, incluindo instrumento específico para avaliação de religiosidade, espiritualidade e crenças pessoais dos pacientes (WHOQOL-SRPB) (Panzini, Maganha, Rocha, Bandeira, & Fleck, 2011). O WHOQOL-SRPB possui como fator relevante o seu desenvolvimento a partir de estudos de campo e validação de construtos em 18 diferentes países com indivíduos de diversas culturas, crenças e religiões, e identifica 8 domínios ligados a R/E que possuem maior contribuição para qualidade de vida (Zimpel et al., 2009):

a) Conexão com ser ou força espiritual: "até que ponto alguma conexão com um ser espiritual ajuda você a passar por épocas difíceis?"
b) Sentido na vida: "até que ponto você sente que sua vida tem uma finalidade?"
c) Admiração: "até que ponto você consegue ter admiração pelas coisas ao seu redor? (p. ex., natureza, arte, música)"
d) Totalidade e integração: "quão satisfeito você está por ter um equilíbrio entre a mente, o corpo e a alma?
e) Força espiritual: "o quanto a força espiritual o ajuda a viver melhor?"
f) Paz interior: "até que ponto você sente paz interior?"
g) Esperança: "até que ponto você está esperançoso com sua vida?"
h) Fé: "até que ponto a fé lhe dá conforto no dia-a-dia?"

Versões recentes e abreviadas do instrumento, também validadas para o português brasileiro, permitem a avaliação dos 8 domínios do WHOQOL-SRPB com 26 itens e 9

itens em versão mais recente, aprimorando a possibilidade de estudo em pesquisas sobre o tema (Skevington et al., 2013; Zimpel et.al, 2019) .

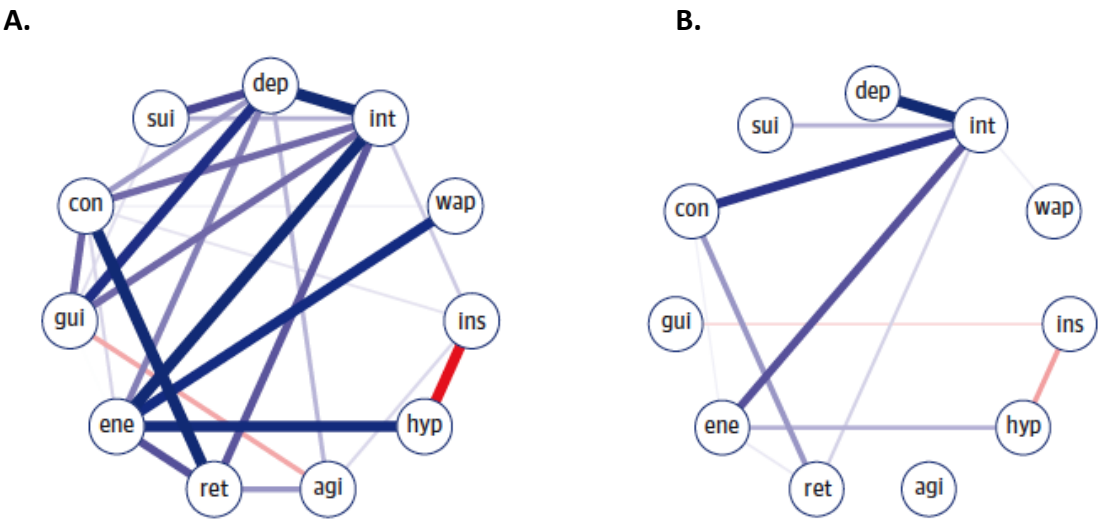

Figura 1. Análise de Rede de pacientes com depressão comparando respondedores (B) e não respondedores (A) ao tratamento, demonstrando conexões diversas entre sintomas depressivos avaliados. Conexões em azul indicam associações diretas, conexões em vermelho inversas entre sintomas. A espessura das conexões *(edges)* representa graficamente a força de conexão entre as variáveis estudadas (*nodes).* O estudo referido demonstra maior conexão entre as variáveis na rede A (pacientes que não responderam ao tratamento) comparados com a rede B (pacientes respondedores), e exemplifica graficamente o diferente peso ou centralidade de cada sintoma de depressão para o conjunto completo de sintomas depressivos. Abreviaturas: *Dep=depressed mood, Int=loss of interest or pleasure, Wap=weight/appetite change, Ins=insomnia, Hyp=hypersomnia, Agi=psychomotor agitation, Ret=psychomotor retardation, Ene=fatigue or loss of energy, Gui=feelings of guily, Con=concentration, decision making, Sui=suicidality* (Van Borkulo et al., 2015).

2.2. Religiosidade, Espiritualidade e Depressão

2.2.1. Definições

Não existem descrições únicas para os conceitos de religiosidade e espiritualidade. A própria distinção entre os termos é algo relativamente novo em termos históricos e ocorre ao longo do século XX, na medida da percepção de que poderia haver espiritualidade sem religião, especialmente em culturas ocidentais e seculares (King & Koenig, 2009).

Entretanto, uma das definições de religiosidade e espiritualidade mais utilizadas, particularmente em pesquisas na área da saúde, compreende a religião como "*o sistema organizado de crenças, práticas, rituais e símbolos designados para facilitar a aproximação com experiências do sagrado ou transcendente"*. Espiritualidade, por sua vez, é compreendida como "*a busca pessoal de respostas para questões ligadas a vida, significado existencial e relação com o sagrado ou transcendente, que pode ou não levar a rituais religiosos ou experiências em comunidade"* (Koenig et al., 2012). Considerando a proximidade entre os conceitos, comumente encontramos a expressão religiosidade/espiritualidade (R/E) para se referir de forma mais ampla a ambos termos.

De qualquer forma, atualmente, a religiosidade e espiritualidade são entendidos como conceitos multidimensionais (Kendler et al., 2003). Entre os principais domínios da R/E identificamos, por exemplo, na escala de religiosidade de Duke, a religiosidade organizacional (frequência a encontros religiosos), religiosidade não-organizacional (práticas religiosas privadas como leituras, preces, meditação) e religiosidade intrínseca (grau de envolvimento e presença da religiosidade na vida pessoal) (Taunay et al., 2012). Outras dimensões da religiosidade e espiritualidade são avaliadas, por exemplo, na escala de coping religioso/espiritual, escala de bem-estar espiritual ou no instrumento WHOQOL-SRPB para avaliação da qualidade de vida ligada a espiritualidade e crenças pessoais da OMS (Panzini et al., 2011). Para avaliação mais aprofundada do instrumentos para mensuração da R/E sugerimos revisão de Lucchetti e col. com escalas disponíveis com validação em português para população brasileira (Lucchetti et al., 2013).

2.2.2. Epidemiologia e Impacto sobre a Saúde Mental

A religiosidade e espiritualidade constituem tema de grande interesse na população em geral (Pargament & Lomax, 2013). Dados epidemiológicos do instituto *Pew Research Center*, por exemplo, identificam que no mundo 83,7% da população mundial (6,9 bilhões de pessoas) possuem afiliação a grupos religiosos e a maior parte das pessoas sem afiliação declaram crenças ligadas a fé e espiritualidade (Hackett et al., 2012). No Brasil, em

levantamento representativo da população, 83,4% dos adultos declaram que a religiosidade constitui algo muito importante em suas vidas (Moreira-Almeida et al., 2010).

Além do mais, boa parte das pessoas demonstram interesse na abordagem de sua espiritualidade nos atendimentos em saúde (Heyland et al., 2006). Aspecto interessante é que a abordagem da espiritualidade na prática clínica pode aumentar a percepção dos pacientes sobre satisfação com os tratamentos (Koenig et al., 2020; Moreira-Almeida et al., 2014).

Embora em geral psiquiatras apresentem menor envolvimento religioso comparados com a população geral, a maior a parte dos profissionais reconhece a importância da abordagem do tema na prática clínica. Estudo com 484 psiquiatras brasileiros, por exemplo, refere que 66,7% dos psiquiatras possuem uma afiliação religiosa e 76,8% dos profissionais consideram importante a integração da R/E nos atendimentos. Entretanto, 55.5% dos profissionais não questionavam rotineiramente os pacientes sobre o tema. Entre as principais barreiras para abordagem do tema na prática clínica foram identificados: falta de tempo (17,1%), dúvidas quanto ao papel profissional e receio de ultrapassar limites éticos (30,2%) e falta de treinamento durante a formação médica sobre R/E (22,3%) (Menegatti-Chequini et al., 2016).

Nesse sentido, diversas iniciativas em associações de vários países tem proposto sessões de estudo e pesquisa sobre religiosidade e espiritualidade e saúde mental, incluindo, por exemplo, Associação Americana de Psiquiatria (*APA Caucus on Religion, Spirituality and Psychiatry*), Associação Britânica de Psiquiatria (*Spirituality and Psychiatry Special Interest Group do Royal College of Psychiatrists*), Associação Brasileira de Psiquiatria (Seção de Estudos e Pesquisas sobre Espiritualidade e Psiquiatria da ABP) e Associação Mundial de Psiquiatria (*World Psychiatric Association* ou WPA) (Moreira-Almeida et al., 2014).

Conforme a diretrizes da WPA (*Position Statement on Spirituality and Religion in Psychiatry*) a religiosidade e espiritualidade devem ser consideradas em diversos contextos e de forma integrada desde a avaliação, diagnóstico, pesquisa, educação e tratamento psiquiátricos (ver tabela 1) (Moreira-Almeida et al.,2016).

Tabela 1. Diretrizes da WPA para Abordagem da Religiosidade/Espiritualidade na Psiquiatria*

(1) Uma consideração cuidadosa das crenças e práticas religiosas dos pacientes, bem como da sua espiritualidade, deveria ser feita rotineiramente, sendo, por vezes, um componente essencial da coleta da história psiquiátrica;
(2) A compreensão da R/E e sua relação com o diagnóstico, etiologia e tratamento de transtornos psiquiátricos devem ser consideradas como componentes essenciais tanto

da formação psiquiátrica como do contínuo desenvolvimento profissional.

(3) Há uma necessidade de mais pesquisas sobre R/E em psiquiatria, especialmente sobre suas aplicações clínicas. Esses estudos devem abranger uma ampla diversidade de contextos culturais e geográficos.

(4) A abordagem de R/E deve ser centrada na pessoa. Psiquiatras não devem usar sua posição profissional para fazer proselitismo de visões de mundo seculares ou espirituais. Devem sempre respeitar e ser sensíveis às crenças e práticas espirituais/religiosas de seus pacientes, assim como das famílias e cuidadores de seus pacientes.

(5) Os psiquiatras, sejam quais forem suas crenças pessoais, devem estar dispostos a trabalhar com líderes/membros de comunidades religiosas, capelães e agentes pastorais, bem como outros membros da comunidade, em suporte ao bem-estar de seus pacientes, incentivando seus colegas multidisciplinares a fazerem o mesmo.

(6) Os psiquiatras devem demonstrar consciência, respeito e sensibilidade quanto ao importante papel que R/E podem desempenhar, para muitos funcionários e voluntários, na formação de uma vocação para trabalhar no campo dos cuidados em saúde mental.

(7) Os psiquiatras devem estar cientes do potencial tanto benéfico quanto prejudicial das práticas e visões de mundo religiosas, espirituais e seculares, e devem estar dispostos a compartilhar essas informações de forma crítica e imparcial com a comunidade em geral, em apoio à promoção da saúde e bem-estar .

http://religionandpsychiatry.org/main/wpa-position-statement-on-spirituality-and-religion-in-psychiatry/

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*Position Statement da WPA sobre Religiosidade, Espiritualidade e Psiquiatria versão em português (Moreira-Almeida et al.,2016)

Nas últimas décadas crescente número de estudos científicos têm procurado compreender o efeitos da R/E sobre a saúde e especialmente na psiquiatria e saúde mental (Koenig et al., 2012; Rosmarin et al., 2020). Em geral, níveis maiores de R/E têm sido associados a melhor prognóstico na depressão, transtorno bipolar, transtornos por uso de substâncias, menor risco de suicídio e maiores níveis de bem-estar e qualidade de vida (Bonelli & Koenig, 2013; Panzini et al., 2017). Por outro lado, efeitos negativos ou prejudiciais da religiosidade (e.g. *coping religioso/espiritual* negativo, conflitos religiosos, religiosidade imatura e fanatismos religiosos) tem sido descritos e devem fazer parte do entendimento do tema e avaliação psiquiátrica (Pargament et al., 1998).

Um dos maiores desafios do estudo da R/E, entretanto, é compreender de que forma a R/E é capaz de influenciar de forma positiva ou negativa a saúde mental (Koenig et al., 2012). A compreensão dos mecanismos ou mediadores de efeito da R/E tem sido diretriz central de estudos e pesquisas recentes sobre o tema (Svob et al., 2019).

Além disso, estudos de revisão estimam que boa parte das pesquisas ligadas a R/E e saúde (75%) são provenientes de países da Europa e América do Norte (Koenig et al., 2012). Nesse sentido, estudos em outros países, culturas e contextos religiosos, incluindo América Latina e no Brasil particularmente, fazem-se necessários para aprimorar entendimento do tema incluindo outras perspectivas culturais.

2.2.3. Religiosidade, Espiritualidade e Depressão

Evidências consistentes identificam que em geral pacientes com maior religiosidade apresentam recuperação mais rápida de sintomas depressivos e menor incidência de depressão em estudos prospectivos (Koenig et al., 1998; Miller et al., 2012; Mosqueiro et al., 2020).

Revisão sistemática de Smith e col., por exemplo, incluindo 147 estudos sobre depressão e religiosidade (n=98,975) relata uma correlação geral inversa da religiosidade com sintomas depressivos (r= -0,096). Uma correlação maior, entretanto, foi identificada quando considerado o efeito da religiosidade intrínseca (r=-0,17) e em pacientes que se encontravam em situações de estresse e adversidade (r=-0,15) (Smith et al., 2003).

Em revisão mais recente de Braam e col. incluindo 152 estudos prospectivos sobre R/E e depressão (n=232.867), 49% dos estudos identificaram associação geral de maior religiosidade com menor depressão, em 10% dos estudos com maior depressão e em 41% dos estudos não houve associação entre as variáveis. Em geral a correlação das medidas gerais de religiosidade com depressão foi modesta (d=-0,18), apresentando maior efeito protetor para grupos de pacientes psiquiátricos (d=-0,37) (Braam & Koenig, 2019).

Estudos recentes também identificam que existe um significativo efeito protetor da religiosidade para o risco de suicídio, incluindo estudos em pacientes graves em internação psiquiátrica (Fazel & Runeson, 2020; Mosqueiro et al., 2015). Estudo prospectivo com alto rigor metodológico avaliando 48.984 mulheres nos Estados Unidos, por exemplo, identificou que maior frequência encontros religiosos foi relacionado a risco 84% menor de suicídio ao longo do período seguimento (OR 0.16), controlando-se o efeito para variáveis importantes como sintomas depressivos e suporte social (VanderWeele et al., 2016).

2.2.4. Religiosidade, Espiritualidade e Marcadores Biológicos

Medidas diversas de religiosidade/espiritualidade tem sido relacionadas a correlatos biológicos em pesquisas clínicas. Entre os objetivos desses estudos encontram-se compreender possíveis mediadores de efeito da religiosidade/espiritualidade com efeitos

positivos em saúde e avaliar possíveis predisposições biológicas em pacientes com maior religiosidade. Um dos primeiros estudos sobre o tema relata relações entre maior religiosidade e menores níveis de interleucina-6 em pacientes com mais de 65 anos nos Estados Unidos (n=1718) (Koenig et al., 1997). Pesquisas recentes também relatam correlações entre maior religiosidade e maior comprimento de telômeros (encurtamento dos telômeros tem sido associados a envelhecimento, morte celular e maior risco de demência) (Wang et al., 2019).

Em revisão de estudos de neuroimagem, diferentes áreas cerebrais parecem apresentar ativação diversa em pacientes com maior envolvimento com religiosidade e espiritualidade e experiências espirituais, incluindo áreas como córtex medial frontal, córtex orbitofrontal, precúneo, córtex cingulado posterior e caudado (Beauregard & Paquette, 2006; Rim et al., 2019).

Em pacientes com depressão, pesquisas tem procurado compreender de que forma efeitos positivos da R/E podem ser traduzidos em marcadores ou desfechos biológicos. Estudo com seguimento de 10 anos, por exemplo, identificou que pessoas que declaravam maior importância para religiosidade apresentavam um quarto do risco de apresentar episódios depressivos no seguimento (OR 0,24), com fator protetor ainda maior, um décimo do risco (OR 0,09), em indivíduos com histórico familiar de depressão (Miller et al., 2012). No mesmo grupo de pacientes, indivíduos que relatavam maior importância na religiosidade em suas vidas apresentavam maior espessura cortical em diversas áreas, possivelmente correspondentes ao fator protetor para depressão (Miller et al., 2014). Em outro estudo, maior religiosidade também foi relacionado a menor conectividade cerebral em *default mode network* (DMN), padrão identificado a menor risco de depressão em outros estudos (Svob et al., 2016)

2.2.5. Mediadores de Efeito da Religiosidade e Espiritualidade

Um dos principais desafios para pesquisa é compreender de que forma a R/E pode exercer seus efeitos em pacientes com depressão. Diversos fatores tem sido descritos como possíveis mediadores de efeito da R/E sobre saúde mental e depressão. No entanto, não existe modelo ou fator único capaz de explicar de que forma a R/E exerce seus efeitos em saúde mental.

Os efeitos positivos da R/E na depressão identificados nos estudos tem sido relacionados a diversos fatores (ver tabela 2). Entre os principais mecanismos explicativos podemos citar desde os efeitos comportamentais ligados a prática religiosa individual (e.g. preces, meditação, leituras com conteúdo religioso-espiritual) (Anderson & Nunnelley, 2016) a efeitos relacionados a frequência a encontros religiosos (e.g. efeito de ativação

comportamental diante de compromissos regulares, maior suporte social, e benefícios relacionados a práticas voluntárias) (Li et al., 2016; VanderWeele et al., 2019) até fatores subjetivos com efeito positivo sobre a saúde mental, como sentimentos de otimismo, fé, esperança, força e bem-estar espiritual relacionados às práticas religiosas (Jeste et al., 2015). Comportamentos estimulados por grupos religiosos incluindo maiores cuidados com a saúde, menor uso de álcool, tabagismo e uso de drogas, parecem contribuir para saúde física e mental (Koenig et al., 2020). Construtos específicos como resiliência, crescimento pós-traumático e coping religioso-espiritual positivo, por sua vez, tem sido estudados para compreensão da capacidade da R/E como recurso de auxílio diante de situações adversas e estressores (Mosqueiro et al., 2015). A ideia da existência de um sentido ou propósito de vida, ou mesmo um senso de coerência diante da vida para compreender acontecimentos, gerando sentimentos de segurança, confiança e auto-eficácia, também tem sido estudados (Anyfantakis et al., 2015; Jeste et al., 2015).

Diferenças genéticas e em expressão de marcadores biológicos também tem sido relacionados aos efeitos protetores da R/E na depressão. Nessa perspectiva, indivíduos com maior religiosidade apresentariam diferenças genéticas e correlatos neurobiológicos com efeitos protetores para depressão (Miller et al., 2012). De acordo com essa hipótese, estudos genéticos identificam que parte da religiosidade apresenta herdabilidade genética (Kendler et al., 2003). Diversos estudos recentes relacionam maior R/E a marcadores biológicos como interleucina-6, fatores imunológicos e diferenças em exames de neuroimagem cerebral (e.g. espessura cortical, *default mode network).*

Sem dúvida, a diversidade de expressão das crenças, práticas, e contextos culturais, além das diversas dimensões de R/E, aumentam a complexidade do tema e o desafio para compreender como ocorrem seus efeitos. Variáveis individuais ligadas a personalidade, maturidade emocional, experiências espirituais e desenvolvimento na infância e adolescência são outros fatores ainda pouco compreendidos, mas que podem certamente apresentar influências sobre efeitos positivos e negativos da R/E na saúde mental. James Fowler, nesse sentido, a partir dos modelos de Erik Erickson, aborda possíveis estágios do desenvolvimento da fé e religiosidade, desde suas expressões mais infantis e autocentradas nos primeiros estágios até a fé e religiosidade como sentimento universal (Fowler, 1981).

Tabela 2. Principais fatores estudados para explicar efeitos positivos da R/E na depressão.

(1) Efeitos positivos sobre sintomas depressivos e ansiosos de práticas e rituais religiosos como preces, meditações, leituras (Anderson & Nunnelley, 2016).
(2) Efeitos comportamentais com frequência regular a encontros religiosos (Li et al., 2016).
(3) Presença de maior suporte social, convivência interpessoal e sentimento de pertencimento a grupos religiosos (Moreira-Almeida et al., 2011).
(4) Visões de mundo e senso de coerência compartilhados com efeito protetor a estressores e adversidades (Anyfantakis et al., 2015).
(5) Estratégias de *coping* ou *enfrentamento* com conteúdo religioso/espiritual (Pargament et al., 2000).
(6) Estímulos e desenvolvimento de fatores positivos como resiliência, gratidão, esperança, propósito existencial e otimismo (Jeste et al., 2015).
(7) Maturidade do sentimento religioso e desenvolvimento emocional (Fowler, 1981).
(8) Estímulos a ações comunitárias, convivência solidária e altruísmo (VanderWeele et al., 2019).
(9) Estímulos a hábitos e comportamentos saudáveis, com menor exposição a riscos, menor uso de álcool, tabagismo, substâncias (Koenig et al., 2012).
(10) Predisposições, diferenças genéticas e marcadores biológicos em grupos de indivíduos com maior religiosidade, com efeitos protetores para saúde mental (Miller et al., 2012).

2.2.6. Prática Clínica

Considerando a importância epidemiológica do tema e seu impacto no diagnóstico e tratamento psiquiátrico, a avaliação de aspectos ligados a R/E deve ser avaliada como rotina e integrada de forma ativa nos atendimentos na área de saúde mental (Koenig et al., 2020).

Diretrizes para avaliação da R/E salientam a importância de uma abordagem centrada no paciente, sem proselitismo e atenta para fatores pessoais dos profissionais que possam dificultar a avaliação do tema, a favor ou contra experiências religiosas ou espirituais (Moreira-Almeida et al., 2014). Além disso, a avaliação clínica deve ser realizada de forma respeitosa, sensível, e aberta a diversas particularidades e diferenças culturais dos pacientes (Moreira-Almeida et al., 2016).

A abordagem compreensiva e adequada da R/E do pacientes pode ser fator importante para adesão aos tratamentos e decisiva no fortalecimento de vínculos com profissional da saúde para muitos pacientes (Pargament & Lomax, 2013). Nesse sentido, as psicoterapias integradas a espiritualidade (*Spiritually Integrated Psychotherapy*), que incluem aspectos culturais ligados a R/E no contexto de psicoterapias convencionais, tem sido estudadas como estratégias relevantes para pacientes que demonstram interesse sobre o tema (Rosmarin et al., 2015). Estratégias e modelos para abordagem da espiritualidade em

psicoterapia tem sido descritas para terapias cognitivo-comportamentais (Lim et al., 2014; Snaith et al., 2018), terapia interpessoal (Mastropieri et al., 2015) e psicoterapias de orientação analítica (Lomax et al., 2011), entre outras.

Evidências científicas de ECR demonstram a eficácia de modelos de TCC integrada a religiosidade/espiritualidade comparados a modelos convencionais de TCC, com benefícios adicionais esperados na adesão e bem-estar para pacientes com maior envolvimento com o tema (Anderson et al., 2015).

A integração da religiosidade e espiritualidade na psicoterapia e prática clínica podem contribuir no processo no atendimento dos pacientes: (1) como forma de conhecer melhor os indivíduos, incluindo aspectos de grande importância relacionados a cultura, crenças, identidade, conflitos e recursos internos; (2) como desfechos integrados aos objetivos dos tratamentos, incluindo melhora no bem-estar espiritual, fortalecimento de estratégias de *coping* positivas e desenvolvimento da relação do indivíduo com sua espiritualidade de forma construtiva, criativa e madura; (3) como elemento facilitador a outras formas de tratamento, como por exemplo, frequência a encontros religiosos como recurso de ativação comportamental no tratamento da depressão, uso de conteúdos R/E no questionamento de pensamentos disfuncionais na TCC ou conteúdos ligados a R/E do paciente integrados a práticas de *mindfulness*; (4) como perspectiva mais ampliada no processo psicoterápico, entendendo a espiritualidade como parte do *self* e desenvolvimento pessoal (Captari et al., 2018).

A abordagem de possíveis conflitos ligados a religiosidade (*religious struggles)* ou estratégias de enfrentamento R/E não adaptativas *(coping religioso-espiritual negativo)* representam importantes aspecto no atendimento de pacientes com efeitos negativos ligados a R/E (Pargament et al., 2005). Além do mais, o reconhecimento dos fatores positivos ligados a religiosidade e espiritualidade, a partir das evidências disponíveis (e.g. *coping religioso-espiritual positivo, religiosidade intrínseca, frequência regular a encontros religiosos)* constituem recursos relevantes que podem ser fortalecidos e encorajados no atendimento de muitos pacientes na prática clínica (Mosqueiro et al., 2020).

4. OBJETIVOS

4.1. Objetivo Geral

Estudar o impacto da religiosidade e espiritualidade no tratamento da depressão em pacientes atendidos no ambulatório de transtornos de humor e internação psiquiátrica do Hospital de Clínicas de Porto Alegre.

4. 2. Objetivos Específicos

- Avaliar o impacto da R/E em um marcador de neuroplasticidade cerebral (BDNF) em pacientes com depressão atendidos na Unidade de Internação Psiquiátrica do HCPA (Artigo #1).

- Avaliar as relações entre domínios da R/E, fatores positivos e sintomas depressivos através de análise de rede (*network analysis*) de pacientes com depressão atendidos no ambulatório de transtornos de humor PROTHUM-HCPA (Artigo #2)

- Avaliar o impacto da R/E no risco de suicídio de pacientes com depressão atendidos no ambulatório de transtornos de humor PROTHUM-HCPA (Artigo #3)

- Avaliar o impacto da R/E na remissão de sintomas depressivos em 6 meses de seguimento de pacientes com depressão atendidos no ambulatório de transtornos de humor (PROTHUM-HCPA) (Artigo #3)

- Avaliar a percepção dos pacientes sobre R/E e interesse sobre integração da R/E no seu tratamento da depressão no ambulatório de transtornos de humor PROTHUM-HCPA (Artigo #4)

5. HIPÓTESES

5.1 A religiosidade e espiritualidade constituem tema de grande importância para os pacientes com depressão atendidos no HCPA, e a maior parte dos mesmos apresenta interesse na integração desses temas em seu tratamento para depressão.

5.2 A religiosidade e espiritualidade são construtos multidimensionais e fatores positivos como resiliência, suporte social, podem ser mediadores de efeito sobre desfechos clínicos em pacientes com depressão.

5.3 Pacientes com maior religiosidade apresentam menor risco de suicídio e maiores chances de remissão dos sintomas depressivos em seguimento prospectivo ambulatorial.

5.4. Pacientes com maior religiosidade apresentam maiores níveis séricos de BDNF, possível marcador biológico de neuroplasticidade e recuperação em pacientes com depressão.

6. CONSIDERAÇÕES ÉTICAS

Todos indivíduos participantes dos estudos apresentados na presente tese apresentam termo de consentimento livre e esclarecido, atendendo aos compromissos bioéticos de autonomia, beneficência, não-maleficência, veracidade e confidencialidade, e encontram-se vinculados aos seguintes projetos:

- "Caracterização de subgrupos de pacientes com depressão maior baseado na curso, sintomatologia, biomarcadores, e resposta a tratamento" (GPPG 160540) desenvolvido no ambulatório PROTHUM do Hospital de Clínicas de Porto Alegre, e aprovado junto Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre.

- "Avaliação e seguimento de pacientes com doença mental severa: fatores diagnósticos, prognósticos e de tratamento e sua associação com marcadores biológicos" (GPPG 10265), desenvolvido na unidade de internação psiquiátrica do Hospital de Clínicas de Porto Alegre, e aprovado junto Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre.

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Increased levels of brain-derived neurotrophic factor are associated with high intrinsic religiosity among depressed inpatients

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Increased levels of brain-derived neurotrophic factor are associated with high intrinsic religiosity among depressed inpatients

Abstract

Recognition of the importance of religion and spirituality in psychiatry is increasing, and several studies have shown a predominantly inverse relationship between religiosity and depression. Brain-derived neurotrophic factor (BDNF) is a widely studied brain neurotrophin responsible for synaptic plasticity, dendritic and neuronal fiber growth, and neuronal survival. The objective of the present study was to evaluate BDNF levels across high and low intrinsic religiosity (IR) in depressed inpatients. Serum BDNF levels were evaluated from 101 depressed inpatients at hospital admission and 91 inpatients at discharge. Religiosity was assessed using a validated version of the Duke University Religion Index. High IR patients had significantly higher serum BDNF at discharge compared to low IR (52.0 versus 41.3 ng/mL, $P = 0.02$), with a Cohen's *d* effect size difference of 0.56. Paired t-test analysis showed that high IR patients had a statistically significant increase in BDNF levels from admission to discharge (43.6 ± 22.4 versus 53.8 ± 20.6 ng/mL, -1.950 (*t*-statistic), $P = 0.05$, Table 2). The relationship between IR and BDNF levels (F=6.199, p=0.00), was controlled for the effects of depressive symptoms ($\beta = 2.73$, $P = 0.00$) and psychiatric treatments, including SSRI ($\beta = 0.17$, $P = 0.08$), SNRI ($\beta = -0.23$, $P = 0.02$), TCA ($\beta = -0.17$, $P = 0.10$), lithium ($\beta = 0.29$, $P = 0.00$), anticonvulsants ($\beta = 0.22$, $P = 0.03$), antipsychotics ($\beta = -0.05$, $P = 0.61$), and electroconvulsive therapy ($\beta = 0.00$, $P = 0.98$). The current findings suggest a potential pathway to help understand the protective effect of religiosity in depressive disorders.

Key words: depression; brain-derived neurotrophic factor; religion; spirituality.

Introduction

Over past decades, religion and spirituality have become increasingly important topics in psychiatry research (VanderWeele et al., 2016). Although epidemiological studies in this context have provided evidence for an inverse relationship between religiosity and depression (Harold. G. Koenig et al., 2012), there is limited empirical data on biological correlates that could mediate their relationship (Miller et al., 2012).

Brain-derived neurotrophic factor (BDNF) is one of the most widely studied brain neurotrophins (Kowianski et al., 2018). BDNF influences synaptic plasticity, dendritic and neuronal fiber growth, promotes neuronal survival (Kowianski et al., 2018), and has been proposed as a biological marker of brain neuroplasticity (Polyakova et al., 2015). Meta-analyses have shown that BDNF concentrations are lower in patients with depression compared to healthy controls and that levels increase with successful antidepressant treatment and/or recovery from depression (Kishi et al., 2017).

Previous studies have reported an association between religious attendance and decreased levels of interleukin-6, a pro-inflammatory cytokine linked to higher mortality in older adults as well as depression (H. G. Koenig et al., 1997; Lutgendorf, Russell, Ullrich, Harris, & Wallace, 2004). Other studies have shown that individuals declaring a higher importance for religion or spirituality had a 90% decreased risk of depression and higher cortical thickness (Miller et al., 2014; Miller et al., 2012). Furthermore, higher intrinsic religiosity has been associated with resilience, quality of life, greater improvement of depressive symptoms, and fewer suicide attempts in a sample of depressed inpatients (Bruno Paz Mosqueiro et al., 2015). Nonetheless, to the best of our knowledge, no previous study has yet evaluated whether religiosity correlates with BDNF levels, especially in depressed subjects. Therefore, the aim of the present study was to evaluate whether serum BDNF levels correlate with intrinsic religiosity in a sample of depressed inpatients.

Materials and Methods

Patient sample

The present study evaluated a subset of patients in a prospective cohort study at the Hospital de Clínicas de Porto Alegre, a university hospital and tertiary psychiatric care referral center in southern Brazil. From 634 subjects admitted to inpatient psychiatric care from May 2011 to December 2013, 196 presented with depressive episodes. Of them, serum BDNF levels and complete protocol assessments were consecutively evaluated from 101 depressed inpatients at hospital admission and 91 inpatients at discharge. Written informed consent was obtained from all patients prior to study inclusion according to approval provided by the hospital ethical committee. Patients with clinical comorbidities that could interfere with BDNF analysis (acute or chronic infections, autoimmune or endocrine diseases, neoplasia, etc.), significant cognitive deficits that limited comprehension of self-report instruments, drug or alcohol addiction or dependence as a main diagnostic, and/or current hypomanic or manic episodes were excluded from the present study.

Assessments

Diagnosis of psychiatric disorders was performed using the Brazilian Portuguese version of the Mini International Neuropsychiatric Interview. All subjects meeting criteria for a depressive episode underwent a comprehensive evaluation, including a general protocol with clinical and sociodemographic information and Brazilian Portuguese validated versions of the Hamilton Depression Rating Scale (HAM-D), Cumulative Illness Rating Scale (CIRS), General Assessment of Functioning Scale (GAF), Clinical Global Impression (CGI) Scale, and Brief Psychiatric Rating Scale (BPRS). Resilience scores were evaluated with the Brazilian validated version of the Resilience Scale, a 25-item Likert scale tool with scores ranging from 25 to 175 (higher scores indicate greater resilience). All assessments were performed within the first 72 h of hospital admission and within the 48 h before hospital discharge.

Religiosity

Religiosity was assessed using the Brazilian Portuguese validated version of the Duke University Religion Index (DUREL). The DUREL is a 5-item Likert scale assessment tool with three dimensions of religiosity. The first question evaluates the dimension of organizational religiosity (e.g., church, temple, or institutional attendance), and the second evaluates nonorganizational religiosity (individual religious activities performed in private, such as prayer, religious readings, and meditation). The last three questions comprise the intrinsic

religiosity (IR) dimension, the level of religious commitment and how much religiousness represents a central part of every-day life as a source of belief, motivation, and meaning. IR was chosen as the main dimension of religiosity to predict clinical outcomes in depressed inpatients. Religiosity was accessed at time of hospital discharge, in order to avoid influences of acute psychiatric symptoms at time of admission. Individuals presenting a total score of more than 10 points on the last three questions of the DUREL combined were further categorized into high and low IR groups (Stroppa & Moreira-Almeida, 2013).

BDNF levels

Serum samples were collected within the first 72 h of hospital admission and within the 48 h before discharge. The laboratory research assistants that collect and analyze BDNF serum samples were blinded to clinical and religious measures of depressed patients. Blood samples (10 mL) were drawn by venipuncture into an anticoagulant-free vacuum tube then centrifuged at 4000 × *g* for 10 min. Serum was stored at −80 °C until analysis. BDNF levels in all samples were analyzed by sandwich enzyme-linked immunosorbent assay (ELISA) using the same commercial kit (EMD Millipore Corporation, Billerica, MA, USA). All samples from all patients were analyzed using the commercial kit on the same date. Serum samples in sample diluent (1:100) were incubated on 96-well microtiter plates (flat-bottom), along with BDNF standards (7.8–500 pg BDNF), for 24 h at 4 °C. Plates were then washed four times with wash buffer followed by incubation with a biotinylated mouse antihuman BNDF monoclonal antibody (1:1000 in sample diluent) at room temperature for 3 h. Plates were washed again four times with wash buffer then incubated with a streptavidin-horseradish peroxidase conjugate solution (1:1000 in sample diluent) at room temperature for 1 h. After addition of substrate and stop solution, BDNF content was determined by measuring the absorbance of each sample at 450 nm. The standard curve demonstrates a direct relationship between optical density and BDNF concentration. All BDNF results are expressed in ng/mL.

Statistical analysis

A Kolmogorov-Smirnov (KS) test was applied to assess the normality of the sample distribution. The KS-test indicated that BDNF serum levels at admission (0.89, P=0.40) and discharge (0.72, p=0.67) were normally distributed. First, a Pearson's correlation analysis was performed to evaluate the correlation between scores of intrinsic religiosity and BDNF serum levels at admission and discharge. A one-tailed analysis was conducted to test for the hypothesis of a positive association between variables. Secondly, depressed inpatients categorized into high and low IR groups. A paired t-test analysis was carried out to determine whether the differences between mean BDNF serum levels from admission to

discharge were different across high and low IR groups of depressed inpatients. In the next step, a multivariate analysis of variance was conducted in order to test for the effects of intrinsic religiosity on BDNF samples analyzed on the same time. BDNF levels at admission and discharge were tested as related dependent variables. High and low intrinsic religiosity groups (high IR=1 vs. low IR=0) were analyzed as a categorical independent variable, and the variables age, sex, depressive symptoms at admission, depressive symptoms at discharge, resilience, and tobacco consumption were tested as covariates. A complementary linear regression analysis evaluated the relationship between intrinsic religiosity (high IR=1 vs. low IR=0) and BDNF serum levels at discharge of psychiatric unit, to control for the effects of psychiatric treatments, including selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants (TCA), lithium, anticonvulsants, antipsychotics, and electroconvulsive therapy (ECT). Statistical analyses were performed using SPSS version 20 software. Data are presented as means ± standard deviations or percentages unless specified otherwise.

Results

Sociodemographic and clinical characteristics

Among the depressed inpatients, 59.3% were female, 92.3% were white, and the mean age was 46.2 years-old. Most individuals presented with severe symptomatology in HAM-D, CGI, and BPRS assessments and reported a mean of 2.8 previous psychiatric admissions. There were no statistically significant differences between low and high IR groups across sociodemographic or clinical characteristics, including age, sex, ethnicity, marital status, education, socioeconomic level, number of previous psychiatric hospitalizations, ECT treatment, length of inpatient treatment, prior or current illicit substance use, previous suicide attempts, current tobacco smoking, and clinical scores regarding depressive symptoms (HAM-D), general psychopathology (CGI, BPRS), and functionality (GAF), at admission or discharge (Table 1). High IR patients were more likely to be using SSRI antidepressants at discharge compared to low IR patients (51.4% versus 29.6%, *P* = 0.05).

Religiosity and BDNF levels

A statistically significant correlation between IR and BDNF serum levels was identified at hospital discharge (n=91, r=0.19, 1-tailed, P=0.03, figure 1). The correlation was not statically significant between intrinsic religiosity and BDNF serum levels at admission (n=101, r=0.02, 1-tailed, P=0.41, figure 1).

Comparing categorically IR groups, high IR patients had significantly higher mean serum BDNF levels at discharge compared to low IR patients (52.0 ± 21.3 versus 41.3 ± 16.6 ng/mL, 2.314 (*t*-statistic), *P* = 0.02). Further analysis showed a moderate difference in serum BDNF levels between the IR groups, with a Cohen's *d* effect size difference of 0.56 (Figure 2). On the other hand, no statistically significant differences in serum BDNF levels were found between low and high IR patients at hospital admission (46.4 ± 16.9 versus 45.6 ± 21.7 ng/mL, 0.173 (*t*-statistic), *P* = 0.85). Paired t-test analysis showed that high IR patients had a statistically significant mean increase in BDNF levels from admission to discharge (43.6 ± 22.4 to 53.8 ± 20.6 ng/mL, -1.950 (*t*-statistic), *P* = 0.05, Table 2). On the other hand, no statistically significant differences in BDNF levels were found between admission and discharge in low IR patients (47.6 ± 15.9 to 43.6 ± 19.6 ng/mL, 0.84 (*t*-statistic), *P* = 0.40, Table 2).

A multivariate analysis of variance was performed to test for the interactions between BDNF samples across low and high IR groups at same time, controlling for covariates (table 3). The results showed a significant effect of the independent categorical variable intrinsic religiosity on BDNF levels (Wilks'Lambda 0.754, F(6.199), p<0.01). The effects were significant controlling for age (Wilks'Lambda 0.963, F(0.696), p=0.50), sex (Wilks'Lambda 0.858, F(2975), p=0.06), resilience (Wilks'Lambda 0.832, F (3.646), p=0.03), depressive symptoms at admission (Wilks'Lambda 0.982, F(0.324), p=0.72), depressive symptoms at discharge (Wilks'Lambda 0.865, F(2.816), p=0.06) and tobacco consumption (Wilks'Lambda 0.854, F(3.073), p=0.05). Univariate testing (between-subjects effects) indicated that the effect of intrinsic religiosity was statistically significant at BDNF levels at discharge (F=12.044, p=0.001).

A complementary linear regression model evaluated the effect of psychiatric inpatient treatment at discharge (*n* = 82, R^2 = 0.32, adjusted R^2 = 0.24, *P* = 0.001, Table 4). In this model, IR remained a statistically significant independent variable (β = 0.26, *P* = 0.01) in relationship to serum BDNF levels at hospital discharge, after controlling for SSRI (β = 0.17, *P* = 0.08), serotonin-norepinephrine reuptake inhibitor (β = -0.23, *P* = 0.02), tricyclic antidepressants (β = -0.17, *P* = 0.10), lithium (β = 0.29, *P* = 0.00), anticonvulsants (β = 0.22, *P* = 0.03), antipsychotics (β = -0.05, *P* = 0.61), and ECT (β = 0.00, *P* = 0.98).

Discussion

The present study found higher serum BDNF levels in depressed inpatients with higher IR at the time of discharge from psychiatric hospitalization (F=6.199, p=0.00). This is the first report of an association between religiosity and BDNF, that, among other effects, might be consider a biological marker of neuroplasticity in patients diagnosed with depression. Furthermore, the correlation between IR and higher BDNF levels identified in the present study is consistent with previous reports showing a mainly protective effect of religiosity in depressive disorders (R. Bonelli, Dew, Koenig, Rosmarin, & Vasegh, 2012). A meta-analysis of 147 studies on religion and depression involving an average of 98.975 individuals found an inverse correlation between religiosity and depression, with a larger protective effect among people under severe life stress (Smith et al., 2003). Moreover, prospective studies have confirmed the protective effect of religiosity on incident depression (Miller et al., 2012) and recovery from a depressive episode (Harold G. Koenig et al., 1998). In our previous study, IR was inversely correlated to suicide risk and directly correlated with resilience and quality of life of depressed inpatients (Bruno Paz Mosqueiro et al., 2015). Taken together with the current results, this suggests BDNF may be one pathway mediating the relationship between religiosity and depression.

BDNF promotes neuronal growth, synaptic plasticity, exerts modulatory effects on gray matter in distinct subregions of the prefrontal cortex (Legge et al., 2015), and plays a key role in memory and cognition (Shimada et al., 2014). In depressed patients, BDNF levels are reportedly reduced and increase as symptoms decrease with antidepressant treatment, supporting the neurotrophic hypothesis of depressive disorders (Castren & Kojima, 2017; Polyakova et al., 2015). Increased BDNF levels were also found following short-term meditation in a 6-week randomized clinical trial in nondepressed adults (Gagrani et al., 2018). One hypothesis to be tested would be that religiosity might exert its protective effects against depression by increasing cortical neuroplasticity and neuroprotection through BDNF. Studies have shown that *BDNF* methylation, which decreases *BDNF* transcription, is associated with depressive-like behavior in mice (Tsankova et al., 2006) and depression in humans (Na et al., 2016). Methylation of the *BDNF* promoter was also found to inversely correlate with cortical thickness in depressed individuals (Na et al., 2016). Furthermore, an empirical study reported that a higher religiosity or spirituality was associated with greater cortical thickness in individuals at high-risk for depression (Miller et al., 2014). Hence, the epigenetic mechanism(s) of *BDNF* methylation, providing a link between environment and changes in brain neurobiology, constitutes a promising pathway for understanding how religiosity may alter adult brain function and plasticity (Borrelli, Nestler, Allis, & Sassone-Corsi, 2008).

The relationship between high IR and serum BDNF levels also provides a new route for understanding the biological effects of religiosity on the brain. Previous studies have

shown an association between religious attendance and lower interleukin-6 levels, an inflammatory marker potentially related to depressive disorders (H. G. Koenig et al., 1997; Lutgendorf et al., 2004). A functional magnetic resonance imaging study of Carmelite nuns showed that recollection of spiritual, mystical experiences correlated with increased blood flow in several cortical areas, including the temporal, caudate, cingulate, orbitofrontal, and prefrontal cortices, considered to be associated with religious experiences and positive emotions (Beauregard & Paquette, 2006). The result of other studies evaluating the neurobiological effect of religiosity on depressed individuals also reinforce the relevance of the current findings, reporting higher religious or spiritual importance to be a predictor of decreased default mode network connectivity, a protective biological marker in individuals at high risk for depression (Miller et al., 2014; Connie Svob et al., 2016).

In the present study, high IR consistently remained a statistically significant variable associated to BDNF at hospital discharge after controlling for different potential confounders, including age, sex, resilience, depressive symptoms, and tobacco consumption and psychiatric treatments. Resilience is thought to be one pathway that could explain the effects of intrinsic religiosity in serum BDNF levels. Notably, in our study, the effects of IR on serum BDNF levels were independent of effects of resilience ($F=3646$, $p=0.03$). A recent meta-analysis showed the relationship between stressful life events and depression was significantly moderated by BDNF levels (Hosang et al., 2014). BDNF has also been significantly associated with adaptive stress-coping strategies in a community setting (Aizawa et al., 2015). Alternatively, the effects of IR on BDNF levels might follow a different pathway apart from stress regulation. For example, a genetic epidemiologic study in twins reported that around 37% of religious well-being variance was explained by genetic factors (Tsuang, Williams, Simpson, & Lyons, 2002). An increase in heritable contributions made by personal religiosity could be associated with a decreased risk of major depressive disorder, leading to distinct biological markers of depressive disorders (Miller et al., 2012).

Our conclusions must be interpreted in face of some limitations. The cross-sectional relationship between BDNF levels at hospital discharge and IR do not allow causal inferences between the variables. Multiple neurobiological and psychosocial factors, not controlled in our study, could also interfere with BDNF levels in depressive disorders in an inpatient psychiatric setting. Another set of imitations are associated with potential error rates regarding multiple statistical analysis in a reduced sample size. The results should be considered as preliminary, and replication studies are necessary for further conclusions. Nevertheless, the consistency of findings controlling for relevant potential confounders, including age, sex, resilience, depressive symptoms, tobacco consumption, and the effect of psychiatric treatments, reinforce the relationship between IR and serum BDNF levels.

Conclusion

The present study revealed that depressed inpatients with a higher IR had higher serum BDNF levels at hospital discharge, suggesting a novel pathway to help understand the protective effects of religiosity on the brain with depressive disorders. These findings provide future approaches for investigation of the neuropsychobiological relationship between religiosity and depression.

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Author Contributions Statement

Study conception and design: BPM, MF, NR

Acquisition of data: BPM

Analysis and interpretation of data: BPM, MF, NR

Drafting of manuscript: BPM, MF, NR

Critical revision: BPM, MF, NR

Conflict of Interest Statement

The authors have no conflicts of interest to report.

References

Aizawa, S., Ishitobi, Y., Masuda, K., Inoue, A., Oshita, H., Hirakawa, H., . . . Akiyoshi, J. (2015). Genetic association of the transcription of neuroplasticity-related genes and variation in stress-coping style. *Brain and Behavior, 5*(9), n/a-n/a. doi:10.1002/brb3.360

Beauregard, M., & Paquette, V. (2006). Neural correlates of a mystical experience in Carmelite nuns. *Neurosci Lett, 405*(3), 186-190. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16872743. doi:10.1016/j.neulet.2006.06.060

Bonelli, R., Dew, R. E., Koenig, H. G., Rosmarin, D. H., & Vasegh, S. (2012). Religious and Spiritual Factors in Depression: Review and Integration of the Research. *Depression Research and Treatment, 2012*, 1-8. doi:10.1155/2012/962860

Borrelli, E., Nestler, E. J., Allis, C. D., & Sassone-Corsi, P. (2008). Decoding the Epigenetic Language of Neuronal Plasticity. *Neuron, 60*(6), 961-974. doi:10.1016/j.neuron.2008.10.012

Castren, E., & Kojima, M. (2017). Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. *Neurobiol Dis, 97*(Pt B), 119-126. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27425886. doi:10.1016/j.nbd.2016.07.010

Gagrani, M., Faiq, M. A., Sidhu, T., Dada, R., Yadav, R. K., Sihota, R., . . . Dada, T. (2018). Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: A randomized controlled trial. *Restor Neurol Neurosci, 36*(6), 741-753. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30400122. doi:10.3233/RNN-180857

Hosang, G. M., Shiles, C., Tansey, K. E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC Med, 12*, 7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24433458. doi:10.1186/1741-7015-12-7

Kishi, T., Yoshimura, R., Ikuta, T., & Iwata, N. (2017). Brain-Derived Neurotrophic Factor and Major Depressive Disorder: Evidence from Meta-Analyses. *Front Psychiatry, 8*, 308. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29387021. doi:10.3389/fpsyt.2017.00308

Koenig, H. G., Cohen, H. J., George, L. K., Hays, J. C., Larson, D. B., & Blazer, D. G. (1997). Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. *Int J Psychiatry Med, 27*(3), 233-250. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9565726. doi:10.2190/40NF-Q9Y2-0GG7-4WH6

Koenig, H. G., George, L. K., & Peterson, B. L. (1998). Religiosity and Remission of Depression in Medically Ill Older Patients. *Am J Psychiatry, 155*(4), 536-542. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9546001. doi:10.1176/ajp.155.4.536

Koenig, H. G., King, D. E., & Carson, V. B. (2012). *Handbook of Religion and Health*. New York, NY: Oxford University Press.

Kowianski, P., Lietzau, G., Czuba, E., Waskow, M., Steliga, A., & Morys, J. (2018). BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. *Cell Mol Neurobiol, 38*(3), 579-593. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28623429. doi:10.1007/s10571-017-0510-4

Legge, R. M., Sendi, S., Cole, J. H., Cohen-Woods, S., Costafreda, S. G., Simmons, A., . . . Fu, C. H. (2015). Modulatory effects of brain-derived neurotrophic factor Val66Met polymorphism on prefrontal regions in major depressive disorder. *Br J Psychiatry, 206*(5), 379-384. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25745134. doi:10.1192/bjp.bp.113.143529

Lutgendorf, S. K., Russell, D., Ullrich, P., Harris, T. B., & Wallace, R. (2004). Religious participation, interleukin-6, and mortality in older adults. *Health Psychol, 23*(5), 465-475. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15367066. doi:10.1037/0278-6133.23.5.465

Miller, L., Bansal, R., Wickramaratne, P., Hao, X., Tenke, C. E., Weissman, M. M., & Peterson, B. S. (2014). Neuroanatomical correlates of religiosity and spirituality: a study in adults at high and low familial risk for depression. *JAMA Psychiatry, 71*(2), 128-135. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24369341. doi:10.1001/jamapsychiatry.2013.3067

Miller, L., Wickramaratne, P., Gameroff, M. J., Sage, M., Tenke, C. E., & Weissman, M. M. (2012). Religiosity and major depression in adults at high risk: a ten-year prospective study. *Am J Psychiatry, 169*(1), 89-94. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21865527. doi:10.1176/appi.ajp.2011.10121823

Mosqueiro, B. P., da Rocha, N. S., & Fleck, M. P. d. A. (2015). Intrinsic religiosity, resilience, quality of life, and suicide risk in depressed inpatients. *J Affect Disord, 179*, 128-133. doi:10.1016/j.jad.2015.03.022

Na, K. S., Won, E., Kang, J., Chang, H. S., Yoon, H. K., Tae, W. S., . . . Ham, B. J. (2016). Brain-derived neurotrophic factor promoter methylation and cortical thickness in recurrent major depressive disorder. *Sci Rep, 6*, 21089. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26876488. doi:10.1038/srep21089

Polyakova, M., Stuke, K., Schuemberg, K., Mueller, K., Schoenknecht, P., & Schroeter, M. L. (2015). BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. *J Affect Disord, 174*, 432-440. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25553404. doi:10.1016/j.jad.2014.11.044

Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., . . . Suzuki, T. (2014). A Large, Cross-Sectional Observational Study of Serum BDNF, Cognitive Function, and Mild Cognitive Impairment in the Elderly. *Frontiers in Aging Neuroscience, 6*. doi:10.3389/fnagi.2014.00069

Smith, T. B., McCullough, M. E., & Poll, J. (2003). Religiousness and depression: Evidence for a main effect and the moderating influence of stressful life events. *Psychological Bulletin, 129*(4), 614-636. doi:10.1037/0033-2909.129.4.614

Stroppa, A., & Moreira-Almeida, A. (2013). Religiosity, mood symptoms, and quality of life in bipolar disorder. *Bipolar Disord, 15*(4), 385-393. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23601141. doi:10.1111/bdi.12069

Svob, C., Wang, Z., Weissman, M. M., Wickramaratne, P., & Posner, J. (2016). Religious and spiritual importance moderate relation between default mode network connectivity and familial risk for depression. *Neuroscience Letters, 634*, 94-97. doi:10.1016/j.neulet.2016.10.009

Tsankova, N. M., Berton, O., Renthal, W., Kumar, A., Neve, R. L., & Nestler, E. J. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and

antidepressant action. *Nat Neurosci, 9*(4), 519-525. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16501568. doi:10.1038/nn1659

Tsuang, M. T., Williams, W. M., Simpson, J. C., & Lyons, M. J. (2002). Pilot study of spirituality and mental health in twins. *Am J Psychiatry, 159*(3), 486-488. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11870019. doi:10.1176/appi.ajp.159.3.486

VanderWeele, T. J., Li, S., Tsai, A. C., & Kawachi, I. (2016). Association Between Religious Service Attendance and Lower Suicide Rates Among US Women. *JAMA Psychiatry, 73*(8), 845-851. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27367927. doi:10.1001/jamapsychiatry.2016.1243

Wagnild, G. M. (2014). *The Resilience Scale User's Guide* (P. E. Guinn Ed.). Montana, United States of America: Resilience Center.

Table 1. Socio-Demographic and Clinical Variables in Low and High Intrinsic Religious Depressed Inpatients (n=101)

(%)	Low IR	High IR	Statist*	P-value
Female	33.3%	44.6%	1.033	0.36
Ethnicity				
White	92.6%	81.9%	1.73	0.22
Non-White	7.4%	18.1%		
Marital Status				
Single	34.6%	31.5%		
Married	34.6%	45.2%	1.78	0.61
Separated	23.1%	20.5%		
Widowed	7.7%	2.7%		
Education, years of study				
Occupation				
Student	3.8%	1.4%		
Employed	26.9%	30.6%	1.78	0.93
Unemployed	15.4%	22.2%		
Stay at home	7.7%	4.2%		
Health Insurance	26.9%	26.4%		
Retired	11.5%	8.3%		
Prefer not to mention	7.7%	6.9%		
Performed ECT (yes/no)	44.4%	27.0%	2.77	0.09
Illicit Substance Use Lifetime (yes/no)	22.2%	30.4%	0.44	0.50
Tobacco consumption (yes/no)	45.5%	34.6%	0.77	0.43
Suicide Attempts (yes/no)	66.7%	64.4%	0.04	0.83
Previous Mania	33.3%	33.8%	0.00	0.96
Previous Hypomania	14.8%	8.2%	0.95	0.32
SSRI Discharge	29.6%	51.4%	3.76	**0.05****
TCA Discharge	3.7%	6.8%	0.33	0.56
SNRIs Discharge	11.1%	5.4%	0.99	0.31
Mood stabilizers	22.2%	29.7%	0.55	0.45
Antipsychotics	70.4%	63.5%	0.41	0.52
(Means)	Low IR	High IR	Statist**	P-value
Age	46.5	45.2	0.41 (t)	0.68
Number of Psychiatry Hospital Admissions	2.59	2.99	982.0 (M)	0.97
Length of Inpatient Care in Days	27.5	30.8	962.0 (M)	0.77
Number of Lifetime Suicide Attempts	2.04	1.80	634.0 (M)	0.77
CIRS Global Scores	1.21	1.38	-1.50 (t)	0.13
HAM-D Admission	22.6	23.2	-0.39 (t)	0.69
HAM-D Discharge	8.32	7.26	0.89 (t)	0.37
BPRS Admission	21.5	24.4	-1.23 (t)	0.22
BPRS Discharge	9.73	9.02	0.39 (t)	0.69
CGI Admission	5.00	5.35	659.5 (M)	0.11
CGI Discharge	3.38	3.23	575.5 (M)	0.11
Resilience (RS)	112.0	133.1	-3.10 (t)	**0.00*****

*Chi-Square tests for categorical variables, t-test (t) and Mann-Whitney (M) tests for mean values.
Statistically significant values in bold for p<0.05. * Statistically significant values in bold for p<0.01.

Table 2. Paired t-test analysis of serum BDNF levels (ng/mL) across high and low Intrinsic religiosity groups of depressed inpatients

Intrinsic Religiosity (t-test)	Admission (n=101)	Discharge (n=91)	Statist	P-value
Low IR	46.4 (16.9)	41.3 (16.6)	0.173	0.85
High IR	45.6 (21.7)	52.0 (21.3)	2.314	**0.02**
Intrinsic Religiosity (paired t-test)	Admission	Discharge		
Low IR (n=29)	47.6 (15.9)*	43.6 (19.6)	0.84	0.40
High IR (n=60)	46.3 (22.4)	53.8 (20.6)	-1.950	**0.05**

*Mean values and std. deviation (±SD). *Statistically significant values in bold for P<0.05.

Table 3. Multivariate tests of BDNF serum levels (ng/mL) and intrinsic religiosity in depressed inpatients

Independent variable	Wilks'Lambda	F	Sig.
Intrinsic religiosity (high=1 vs. low=0)	0.754	6.199	0.005**
Covariates			
Age	0.963	0.696	0.50
Sex	0.858	2.975	0.06
Resilience Scale (RS-14)	0.832	3.646	0.03*
Depressive symptoms admission (HAM-D)	0.982	0.324	0.72
Depressive symptoms discharge (HAM-D)	0.865	2.816	0.07
Tobacco consumption	0.854	3.073	0.05*

Multivariate test of BDNF serum levels at time of admission and discharge of depressed inpatients (MANCOVA) | 1. Dependent variables: BDNF serum levels at admission and BDNF serum levels at discharge. 2. Independent variable: high and low intrinsic religiosity (high=1). 3 Covariates: age, sex, resilience scale, HAM-D at admission, HAM-D at dischage, tobacco consumption (yes=1). *Significant for $p<0.05$; **Significant for a $p<0.01$.

Table 4. Multilinear Regression of BDNF serum levels (ng/mL) at hospital discharge in depressed inpatients controlling for psychiatric treatments (n=82)

	Unstandardized Coefficients	Standardized Coefficients	T	Sig.	Colinearity Statistics	
	B	Beta			Tolerance	VIF
Intrinsic Religiosity (Low/High)	11949	0.26	2.635	**0.01**	0.919	1.088
SSRI	7248	0.17	1.731	0.08	0.871	1.149
SNRI	-17.059	-0.23	-2.284	**0.02**	0.876	1.141
TCA	-12.469	-0.17	-1.663	0.10	0.869	1.150
Lithium	16.676	0.29	3.056	**0.00**	0.961	1.041
Anticonvulsants	12.102	0.22	2.196	**0.03**	0.887	1.127
Antipsychotics	-2.327	-0.05	-0.050	0.61	0.925	1.081
ECT	0.112	0.00	0.024	0.98	0.919	1.088

Dependent variable: BDNF serum levels at discharge (R Square 0.32, Adjusted R Square 0.24, p=0.001).

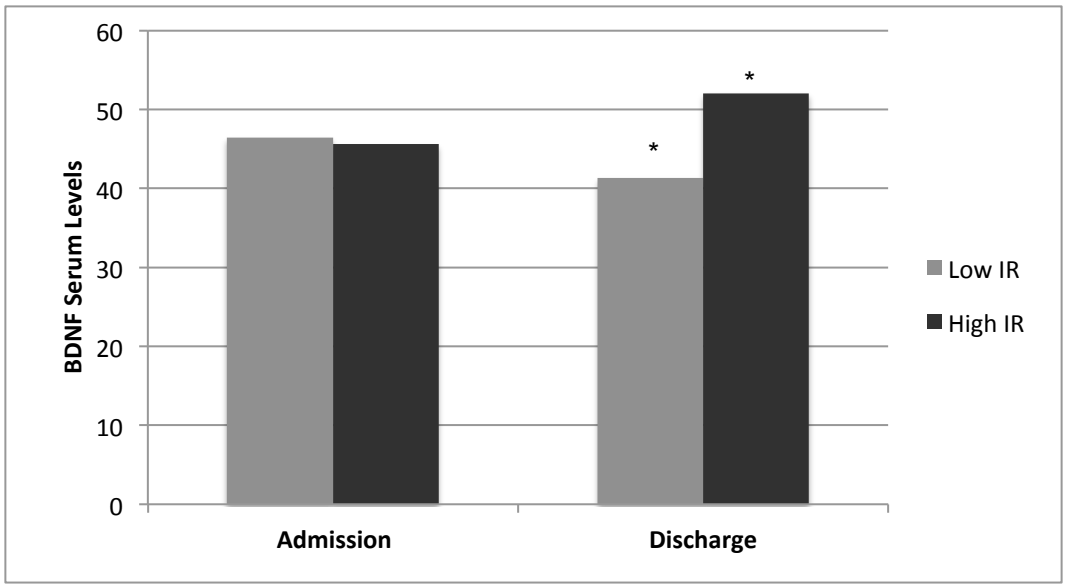
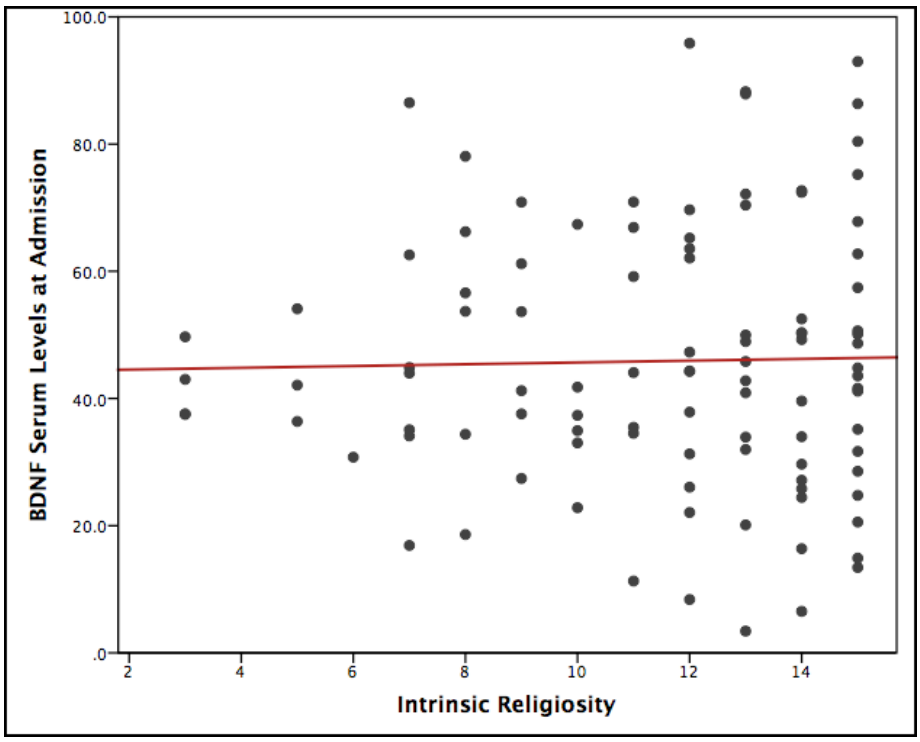


Figure 2. **Intrinsic Religiosity and BDNF serum levels of Depressed Inpatients |** BDNF serum levels (ng/mL) at time of hospital admission (46.4 vs. 45.6, p=0.85, n=101) and discharge (41.3 vs. 52.0, p=0.02, n=91) in Low and High Intrinsic Religiosity Depressed Inpatients. *Statistically significant difference between groups ($p<0.05$).

A.



B.

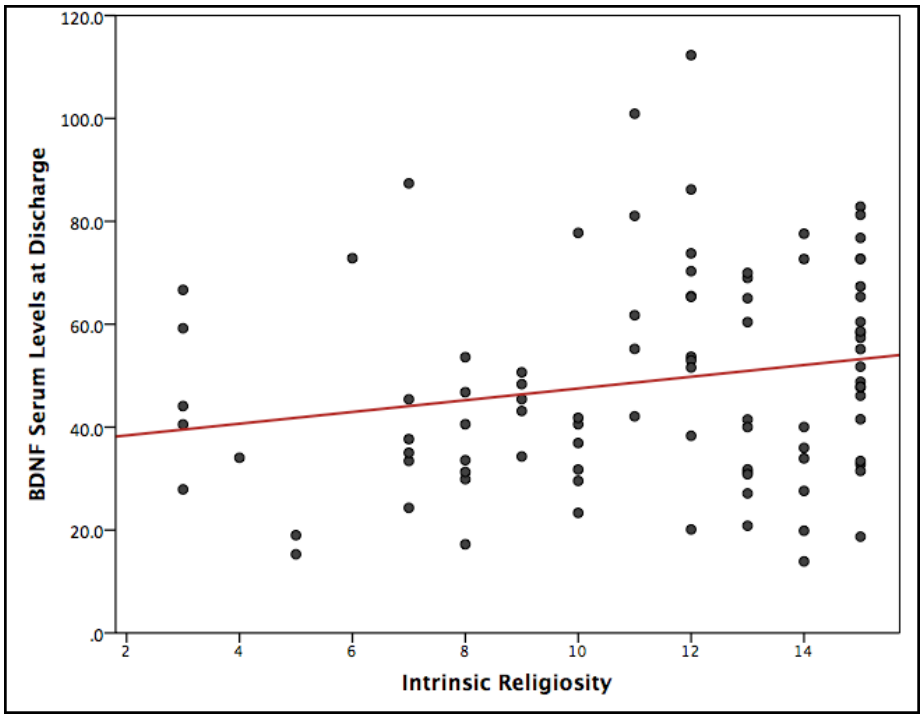


Figure 1. **Scatter plot of correlations between intrinsic religiosity and BDNF serum levels of depressed inpatients |** A. Pearson's correlation coefficient scatter plot of BDNF serum levels (ng/mL) at time of hospital admission (n=101, r=0.02, P=0.41). B. Pearson's correlation coefficients of BDNF serum levels (ng/mL) at time of hospital discharge (n=91, r=0.19, P=0.03).

8. ARTIGO #2

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Exploring Connections between Religiosity/Spirituality, Positive Mental Health, and Depressive Symptoms in Patients with Depression: A Network Analysis Approach

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Carta de Submissão do Artigo para Periódico

A manuscript number has been assigned to Exploring Connections between Religiosity/Spirituality, Positive Mental Health, and Depressive Symptoms in Patients with Depression: A Network Analysis Approach (PSM-D-20-00677)

De: Psychological Medicine (em@editorialmanager.com)

Para: brunopazmosqueiro@yahoo.com.br

Data: quarta-feira, 6 de maio de 2020 21:16 BRT

Dear Dr. Paz Mosqueiro,

Your submission entitled "Exploring Connections between Religiosity/Spirituality, Positive Mental Health, and Depressive Symptoms in Patients with Depression: A Network Analysis Approach" has been been assigned the following manuscript number: PSM-D-20-00677.

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Abstract

Background

Religiosity and spirituality (R/S) are increasingly recognized as significant factors that affect patients with depression. However, there is a lack of information on how R/S dimensions affect clinical outcomes. Network analysis models are useful methods to understand relationships among interacting variables in complex dynamic systems and may be used to determine the effect of R/S dimensions on outcomes.

Methods

The present study evaluated cross-sectional interactions between R/S dimensions, positive mental health factors, and depressive symptoms domains in 153 patients with depression. Assessments were performed with validated versions of the Hamilton Depression Rating Scale (core depression, stress depression, and suicide risk domains), the Duke Religion Index (religious attendance, private practices, and intrinsic religiosity domains), the World Health Organization Quality of Life Religiousness, Spirituality, and Personal Beliefs instrument (WHOQOL-SRPB), the Medical Outcomes Study Social Support Survey (MOS), and the Resilience Scale (RS). Network node connections and estimated centrality measures were tested using R-package mgm.

Results

The strongest network connections were identified between core-depression, suicide risk, resilience, and WHOQOL-SRPB. All religiosity domains were independently related to WHOQOL-SRPB. Suicide risk was positively related to core depression and was inversely correlated with positive mental health measures (resilience, WHOQOL-SRPB total score, WHOQOL-SRPB meaning, and WHOQOL-SRPB awe and social support). Generally, WHOQOL-SRPB had higher centrality measures in the network model and was distributed in the network as central pathways across religiosity domains, depressive symptoms, and other positive mental health constructs (social support and resilience).

Conclusions

The network analysis approach offers a useful method to explore the relationships between R/S and depressive symptomatology. Based on our findings, positive mental health factors play a central role in R/S domains and depression, especially for suicide risk behavior.

Keywords

Depression; religiosity; spirituality; network analysis; positive mental health; suicide

Introduction

Major depressive disorder (MDD) affects 300 million people worldwide and constitutes the leading cause of mental health-related disease burden in the world (Patel et al., 2016). Persistent and recurrent depressive symptoms significantly impact functionality and prevent many individuals from reaching their potential (Herrman et al., 2018). More concerning, depressive disorders account for 59-83% of all deaths by suicide worldwide (Dong et al., 2019). Therefore, understanding the underlying mechanisms associated with MDD and the factors associated with improving outcomes of patients with depression represent a key area of exploration in psychiatry research (Liu et al., 2019).

Network analysis models are methods used to determine relationships among interacting variables in complex dynamic systems (Haslbeck & Waldorp, 2019; Van Borkulo et al., 2015). Recent research that has described different kinds of connections in the network symptoms of MDD (Beard et al., 2016; Cramer et al., 2016) suggests that the strength of global network connections might represent a predictor of treatment response among patients with depression (McElroy et al., 2019; Van Borkulo et al., 2015). Accordingly, network models allow for the following: 1) visual depiction of complex associations among symptoms; 2) data-driven identification of potential pathways among interacting variables in complex systems; 3) identification of highly central or influential symptoms or characteristics that, when activated, might influence other symptoms; and 4) prediction of outcomes according to overall network connectivity between variables (Beard et al., 2016). Furthermore, variables that play a central role in a network with multidimensional relationships might promote a better understanding of the psychopathological mechanisms of MDD and help implement preventive or therapeutic interventions (Cramer et al., 2016).

Religiosity and spirituality (R/S) and positive mental health factors have been increasingly recognized as significant factors in the evaluation of patients with depression (Miller et al., 2012). More than 83.4% of people around the world report affiliation with religious denominations, and religious communities represent a common source of support to many people experiencing mental health conditions worldwide (Hackett et al., 2012; Gureje et al., 2015). Studies have demonstrated that R/S are associated with decreased depressive symptoms and a better course of depression over time (Braam & Koenig, 2019). Furthermore, religious attendance has been identified as a strong protective factor against suicide (VanderWeele et al., 2016). However, there is a gap in understanding how specific R/S dimensions affect clinical outcomes in patients with depression. R/S are multidimensional constructs and R/S measures have been linked with positive mental health factors (e.g., resilience, meaning, hope, purpose, and social support) which may aid in the prevention of and recovery from depression (Kendler et al., 2003; Vance et al., 2014; Jeste et al., 2015; Schiavon et al., 2016).

The present study evaluated network interactions between R/S dimensions, depressive symptoms, and suicide risk and the role of positive mental health factors (e.g., resilience, spiritual quality of life, and social support) as potential pathways between R/S and depression. To the best of our knowledge, this is the first study to explore use of network analysis to gain insights about the complex relationships between R/S dimensions and depression.

Methods

Participants and Treatment Setting

The mood disorder outpatient clinic at Hospital de Clínicas de Porto Alegre (HCPA), a university tertiary care hospital in South Brazil, provides specialized treatment for individuals with chronic, refractory, or severe depressive symptomatology referred to by primary care settings and other outpatient medical clinics. Individuals from this outpatient clinic diagnosed with a depressive episode were consecutively invited to participate in the study. After the first psychiatric evaluation, 153 participants were included in the study from 2014 to 2018. Written informed consent was obtained following approval provided by the hospital ethical committee. Patients with severe clinical comorbidities or individuals with significant cognitive deficits that limited comprehension of self-report instruments and individuals with acute manic or hypomanic episodes were not included.

Depression

Trained psychiatrists diagnosed depressive episodes using the Brazilian Portuguese version of the Mini-International Neuropsychiatric Interview (Amorim, 2000). Depressive symptoms were assessed using the Brazilian Portuguese-validated version Hamilton Depression Rating Scale (HAM-D), which is composed of 17 items (global score: 0 to 52 points). Psychometric analysis of the HAM-D indicate that the 17 items can be reallocated in three dimensions to cover more specific clinical depression domains reflecting: the core symptoms of depression (HAM-D-6: 1, 2, 7, 8, 10, 13), general stress-arousal symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16) and suicide risk behavior (HAM-D-2: 3 and 17) (Bech, 2011). These dimensions were used as nodes for analysis.

Religiosity

Religiosity was assessed using the Brazilian-Portuguese-validated version of the Duke University Religion Index (DUREL) (Taunay et al., 2012). The instrument consists of five Likert-scale questions evaluating three specific dimensions of religiosity. The first question evaluates organizational religiosity or frequency of religious attendance, the second evaluates non-organizational religiosity or the frequency of private practices, such as prayer, meditation, or reading religious content, and the last three compound intrinsic religiosity domain and the level of personal religious faith and commitment to religious beliefs in life. Higher scores after reverse score analysis reflect higher religiosity across all domains.

Spiritual Quality of Life

The World Health Organization Quality of Life Spirituality, Religiousness, and Personal Beliefs instrument (WHOQOL-SRPB) is a multidimensional Likert scale developed as an extension to WHOQOL-100 that has been validated in 18 countries across different cultures and R/S backgrounds (Panzini et al., 2011). The short 8-item version of the WHOQOL-SRPB validated for the Brazilian population was utilized, in which higher scores indicate higher spiritual quality of life. Different items evaluate positive mental health

factors regarding spirituality and quality of life, including the following constructs: (1) connect (the extent that any connection to a spiritual being help through hard times), (2) meaning (the extent that life has a purpose), (3) awe (the extent that faith contribute to wellbeing),
(4) whole (the balance between mind, body, and soul), (5) strength (the extent that spiritual strength helps to live better), (6) peace (the extent of perception of inner peace), (7) hope (the extent of perception of hope about life), and (8) faith (the extent that faith provides comfort in daily life).

Resilience

Resilient psychological characteristics were evaluated with the 14-item version of the Resilience Scale (RS-14), a 7-point Likert scale (scores ranging from 7-98), with higher scores indicating higher resilience. Resilience is defined as the capacity for positive adaptation and recovery in the face of suffering and stressful life events. The Resilience Scale is the first instrument designed to measure resilience directly (Wagnild, 2014).

Social Support

Social support was assessed using the Brazilian validated version of the Medical Outcomes Study Social Support Survey (MOS-SSS), a 28-item Likert scale (5 to 140 points) (Griep et al., 2005). Higher scores indicate a greater perception of social support. The instrument evaluates an individual's perceived availability of emotional support (availability of people expressing positive affect, empathetic understanding, and encouragement), informational support (availability of people offering advice, information, guidance, or feedback), tangible support (availability of people available to provide material or behavioral assistance), positive social interaction (availability of people that can provide fun or recreation), and affectionate support (availability of people who express care and affection).

Analysis

Descriptive analyses were performed to evaluate the clinical and sociodemographic characteristics of the sample. Cross-sectional interactions between R/S and depressive symptoms were subsequently assessed using network analysis models with R software (version 3.5). The R-package mgm (version 1.2) was used for estimation of the k-order Mixed Graphical Model with a 10-fold cross validation. The edition of network models was performed with Cytoscape software (version 3.7.2), which provided a visual representation of connections (edges) between variables (nodes). Green edges were used to indicate positive relationships between variables, red edges to indicate negative relationships, and thicker edges to indicate strong connections between nodes.

Positive mental health factors (psychological resilience, spiritual quality of life, and social support) were tested as potential interacting variables connecting R/S dimensions

(religious attendance, private practices, and intrinsic religiosity) and HAM-D depressive domains (core depression, stress depression, and suicide risk). Strong connections indicate that variables tend to align their states more strongly, controlling for the effects of the other variables in the network (Van Borkulo et al., 2015). Estimate measures of centrality (strength, closeness, and betweenness) were evaluated to understand differences in connectivity between network nodes and identify those variables with a central role in the network.

Centrality measures represent relevant tools to understand more accurately the relevance of studied variables within the whole network dynamic organization. To improve these estimations, different centrality indexes are performed to evaluate the relevance of each node in the network models. The strength index reports how well a node is connected to other nodes (sum of edge weights connected to a node), the closeness index identifies how well a node is indirectly connected to other nodes (inverse of the sum of shortest paths from a node to other nodes), and the betweenness index evaluates how important a node is to connect other nodes (the number of times a node lies on the shortest paths between two other nodes) (Chang et al., 2019). Network statistical analysis (mgm methods) and bootstrap sampling analysis were performed to evaluate network statistical accuracy and stability (Epskamp et al., 2018).

Results

Sample Characteristics

Participants were mainly female (78.2%), white (84.9%), and middle-aged (mean: 51.0±11.2 years). Most participants were unemployed (23.1%) or unable to attend work (35.1%) (Table 1). The mean HAM-D total score was 21.5 (±5.54), indicating a moderate-to-severe episode of depression, with high psychiatric comorbidities and a long course of illness (mean: 18.1±13.8 years since the first episode) with multiple depressive episodes across the lifetime (3.52±2.79). Almost half of the patients reported previous suicide attempts (46.1%), and nearly one-in-four reported a family history of suicide (24.1%). Despite depressive symptomatology, approximately one-third of patients reported attendance to religious groups or institutions at least once a week (33.1%), and most patients had high intrinsic religiosity scores (66.1%). Moreover, assessments revealed significant involvement and interest in religion and spirituality (Table 2).

Network Structure 1

Figure 1 presents the network model structure connecting religiosity domains (religious attendance, private practices, and intrinsic religiosity), WHOQOL-SRPB (total score), social support, resilience, and HAM-D domains (core-depression, stress-depression, and suicide risk). The strongest edges were identified among the following variables: “core depression” and “resilience” (negative correlation), “core depression” and “suicide risk”

(positive correlation), “WHOQOL-SRPB” and “suicide risk” (negative correlation), and “WHOQOL-SRPB” and “resilience” (positive correlation). All religious domains (“religious attendance,” “private practices,” and “intrinsic religiosity”) were independently connected to “WHOQOL-SRPB” (positive correlations). “Intrinsic religiosity” was additionally independently connected to “stress-depression” (negative correlation). “Social support” was independently connected to “WHOQOL-SRPB” (positive correlation) and to “suicide risk” (negative correlation) to a lesser extent.

Depressive symptom nodes were differentially related to other network nodes. “Core depression” was connected (positive correlation) to the other HAM-D dimensions (“suicide risk” and “stress depression”). “Stress-depression” was connected to “intrinsic religiosity” (negative correlation) and “core depression” (positive correlation). “Suicide risk” was connected to “core depression” (positive correlation) and to positive mental health measures (“resilience,” “WHOQOL-SRPB,” and “social support”) (negative correlation) (Figure 1).

Centrality Measures, Network Accuracy, and Stability

Figure 2 shows centrality measures for network 1. The strength measure identified “WHOQOL-SRPB,” “intrinsic religiosity,” “suicide risk,” and “core-depression” as the main network connection nodes. “WHOQOL-SRPB” had higher betweenness and closeness centrality measures scores, reflecting their central indirect connection and pathways to other nodes. Overall, considering strength, closeness, and betweenness, “WHOQOL-SRPB” was identified as the highest centrality measures in the network model. Measures of stability and accuracy of network connections confirmed the relationships reported (Supplementary Materials).

Network Structure 2

A second network analysis was performed to evaluate which WHOQOL-SRPB items were connected to religiosity, social support, resilience, and depressive symptoms (Figure 3). Generally, WHOQOL-SRPB items were distributed in the network as central pathways across religiosity domains, depressive symptoms, and other positive mental health constructs (social support and resilience). Suicide risk domain was directly connected to core depression (positive correlation) and WHOQOL-SRPB meaning and awe (negative correlation). Social support was connected to the WHOQOL-SRPB item peace (positive correlation). Resilience was connected to the WHOQOL-SRPB items peace, hope, awe, and meaning (positive correlation) and strongly connected to core depression (negative correlation).

In network model 2, diverse variables were identified as the highest centrality measures (Figure 4), particularly resilience and WHOQOL-SRPB faith, WHOQOL-SRPB strength, and WHOQOL-SRPB peace.

Discussion

To the extent of our knowledge, this is the first study that evaluated the connections between R/S dimensions and depressive symptoms using a network analysis approach. Based on our findings, R/S dimensions were differentially connected to depressive symptoms. Positive mental health factors (resilience, social support, and WHOQOL-SRPB) represent pathways to explain the positive effects of R/S dimensions (religious attendance, private religious practices, and intrinsic religiosity) on patients with depression.

Studies have shown that positive mental health factors are associated with favorable health outcomes under different health care and community settings (Jeste et al., 2013) A systematic review, for instance, identified that hope was negatively associated with depression and contributed to increased life satisfaction, healthy behaviors, and wellbeing in people with chronic disease (Schiavon et al., 2016). Another study found that hope scores were significantly lower in patients with depression but also among non-depressed individuals with previous depressive episodes, compared to those who had never experienced depression (Thimm et al., 2013).

Resilience, optimism, purpose, and significant relationships with family and religion have been found to be factors associated with good mental health in elderly individuals over 90 years old (Scelzo et al., 2018). Furthermore, a meta-analysis, including a wide range of individuals from different cultures worldwide (N=52,309), demonstrated that positive psychological wellbeing is significantly associated with lower mortality (Chida & Steptoe, 2008). These results are consistent with findings that life purpose was significantly associated with lower all-cause mortality (OR: 2.43) among adults over 50 years old in the US (Alimujiang et. al, 2019). Additionally, there is evidence to support that positive psychological wellbeing is independent of negative affect (Chida & Steptoe, 2008), reinforcing the role of positive mental health factors as valuable ways to improve recovery in patients with psychiatric symptomatology (Galvez et al., 2011; Jeste et al., 2015; Vaillant, 2013; VanderWeele et al., 2019).

A strong and expected positive connection was identified between suicide risk and core depressive symptoms. Psychiatric disorders have the strongest impact on suicide rates, contributing to a 10-fold higher risk compared to general population (Bachmann, 2018). Depression specifically increases the odds of completed suicide by 3-fold (Fazel & Runeson, 2020). WHOQOL-SRPB, however, was found to have the same strength of connection (although negatively correlated) to suicide risk, and, to a lesser extent, resilience and social support were inversely related to suicide risk. Thus, religion, faith, and spirituality represent protective factors against suicide; however, it is important to take into account religious stigma that creates barriers to mental health access in some cultural backgrounds (World-Health-Organization, 2014). Despite this confounding factor, a connection to any religious

affiliation has been reported to be a consistent protective factor against suicide attempts (Lawrence et al., 2016). According to that, a long-term prospective study found that weekly religious attendance was associated with a 5-fold lower rate of suicide among women in the United States (N=89,708) (VanderWeele et al., 2016).

WHOQOL-SRPB meaning and awe, specifically, were most strongly inversely related to suicide risk. These findings may provide potential pathways to understand how positive mental health and spirituality aspects are integrated to depressive symptoms with a network approach. Previous studies, in that regard, reported that hopelessness, loss of meaning, and purpose in life significantly increased suicide risk among psychiatric patients (Berardelli et al., 2019). Positive mental health factors (e.g., self-efficacy, resilience, optimism, and effective problem solving-skills) have been identified as a key protective factors in suicide prevention guidelines (World-Health-Organization, 2014). WHOQOL-SRPB awe could reflect the protective effect of R/S beliefs translated into positive affect or wellbeing (Vaillant, 2013).

Social support was not identified as a central variable in the network connecting religious domains and depressive symptoms. These findings are inconsistent with reports that social support measures are significant predictors of a favorable course of depressive disorder (van den Brink et al., 2018). One possible explanation is that the impact of social support compared to other positive mental health measures in persistently depressed individuals may differ across communities or depression severity (Souza et al., 2016). Moreover, the impact of differing cultural backgrounds is important to understand in determining the effect of social support on depression in Brazil. The role of social support as a key factor in understanding the benefits of religiosity on mental health has not consistently been supported by the literature (Koenig et al., 1997). While religious community support has been associated with fewer reported depressive symptoms, our results are in accordance with studies that identified the effects of religiosity over mental health outcomes independently of social support (Montgomery et al., 2014; Kudel et al., 2011; Li et al., 2016; Mosqueiro et al., 2015).

Network analysis models represent promising methods to understand potential pathways between complex variables and psychopathology. A meta-analysis including 152 prospective studies (N=232,687) confirmed a negative correlation between religiosity and depressive symptoms over time, with an overall effect size correlation of -0.18 (SD: 0.28). In that report, religious attendance was the main dimension measured (45% of studies), followed by importance of religion, religious coping, private practices, and religious denomination (approximately 20% each) (Braam & Koenig, 2019). The negative correlation between R/S and depression was higher for psychiatric samples (r=-0.37), and a positive correlation was identified for patients experiencing religious struggles (r=0.30; SD: 0.36) (Braam & Koenig, 2019). Another meta-analysis showed that the effects of R/S were

stronger for intrinsic religiosity and for people facing stressful life events (Smith et al., 2003). Despite that, few studies have investigated the mechanisms through which R/S exert effects in depressive disorders, as most have not provided an integrated approach to understand the combined effect of different R/S dimensions and depressive symptoms. Additionally, depressive disorders are highly heterogeneous with diverse symptomatology and predisposing risk factors, and improvements triggered by different sets of interventions (e.g., psychopharmacology, psychotherapy, and environment changes) (Vares et al., 2015)Beijers et al., 2019; Ostergaard et al., 2011; Southwick & Charney, 2012). Thus, network analysis models represent an alternative to evaluate the heterogeneity of depressive psychopathology and interactions with relevant variables, including R/S and positive mental health (Van Borkulo et al., 2015). Additionally, network models assume that changes in central symptoms could impact symptomatology, leading to an understanding of specific characteristics of depression and more personalized interventions for patients with depression (Cramer et al., 2016).

The results reported here should be evaluated considering a set of limitations. First, cross-sectional analysis limits causal inferences about relationships. The analysis of severely depressed patients in tertiary outpatient care also limits extending findings to different clinical or community settings. Certainly, findings require replication in larger samples and patients from different cultural and religious backgrounds. Furthermore, the network analysis performed relies on measures and latent class structures of available instruments instead of all depressive symptomatology and measured items individually in the network. However, keeping defined domains in the network according to established validated instruments was thought to be helpful to visualize the complex interplay between those different dimensions of mental health (e.g., resilience, social support, spirituality, and religiosity). A secondary model was performed to visualize how specific WHOQOL-SRPB aspects were related to other studied dimensions. Adding to that analysis, these significant findings provide an integrated data-driven model of interaction between variables and reinforce the relevant role of religiosity and positive mental health to severely depressed patients.

Conclusions

A network analysis approach offers a different perspective to understand the relationships between R/S and depressive symptomatology. Positive mental health factors appear to play a central role between R/S domains and depression, especially for suicide risk behavior.

References

Alimujiang, A., Wiensch, A., Boss, J., Fleischer, N. L., Mondul, A. M., McLean, K., . . . Pearce, C. L. (2019). Association Between Life Purpose and Mortality Among US Adults Older Than 50 Years. *JAMA Netw Open, 2*(5), e194270. doi:10.1001/jamanetworkopen.2019.4270

Amorim, P. (2000). Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev Bras Psiquiat., 22*, 106-115.

Bachmann, S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health, 15*(7). doi:10.3390/ijerph15071425

Beard, C., Millner, A. J., Forgeard, M. J., Fried, E. I., Hsu, K. J., Treadway, M. T., . . . Bjorgvinsson, T. (2016). Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychol Med, 46*(16), 3359-3369. doi:10.1017/S0033291716002300

Bech, P. (2011). The ABC profile of the HAM-D 17. *Rev Bras Psiquiat., 33*, 109-110.

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. *Mol Psychiatry, 24*(6), 888-900. doi:10.1038/s41380-019-0385-5

Berardelli, I., Sarubbi, S., Rogante, E., Hawkins, M., Cocco, G., Erbuto, D., . . . Pompili, M. (2019). The Role of Demoralization and Hopelessness in Suicide Risk in Schizophrenia: A Review of the Literature. *Medicina (Kaunas), 55*(5). doi:10.3390/medicina55050200

Braam, A. W., & Koenig, H. G. (2019). Religion, spirituality and depression in prospective studies: A systematic review. *J Affect Disord, 257*, 428-438. doi:10.1016/j.jad.2019.06.063

Chang, W. C., Wong, C. S. M., Or, P. C. F., Chu, A. O. K., Hui, C. L. M., Chan, S. K. W., . . . Chen, E. Y. H. (2019). Inter-relationships among psychopathology, premorbid adjustment, cognition and psychosocial functioning in first-episode psychosis: a network analysis approach. *Psychol Med*, 1-9. doi:10.1017/S0033291719002113

Chida, Y., & Steptoe, A. (2008). Positive psychological well-being and mortality: a quantitative review of prospective observational studies. *Psychosom Med, 70*(7), 741-756. doi:10.1097/PSY.0b013e31818105ba

Cramer, A. O., Van Borkulo, C. D., Giltay, E. J., Van der Maas, H. L., Kendler, K. S., Scheffer, M., & Borsboom, D. (2016). Major Depression as a Complex Dynamic System. *PLoS One, 11*(12), e0167490. doi:10.1371/journal.pone.0167490

Dong, M., Zeng, L. N., Lu, L., Li, X. H., Ungvari, G. S., Ng, C. H., . . . Xiang, Y. T. (2019). Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. *Psychol Med, 49*(10), 1691-1704. doi:10.1017/S0033291718002301

Epskamp, S., Borsboom, D., & Fried, E. I. (2018). Estimating psychological networks and their accuracy: A tutorial paper. *Behav Res Methods, 50*(1), 195-212. doi:10.3758/s13428-017-0862-1

Fazel, S., & Runeson, B. (2020). Suicide. *N Engl J Med, 382*(3), 266-274. doi:10.1056/NEJMra1902944

Galvez, J. F., Thommi, S., & Ghaemi, S. N. (2011). Positive aspects of mental illness: a review in bipolar disorder. *J Affect Disord, 128*(3), 185-190. doi:10.1016/j.jad.2010.03.017

Griep, R. H., Chor, D., Faerstein, E., Werneck, G. L., & Lopes, C. S. (2005). Construct validity of the Medical Outcomes Study's social support scale adapted to Portuguese in the Pró-Saúde Study. *Cad. Saúde Pública, 21*(3), 703-714. doi:doi: 10.1590/S0102-311X2005000300004

Gureje, O., Nortje, G., Makanjuola, V., Oladeji, B. D., Seedat, S., & Jenkins, R. (2015). The role of global traditional and complementary systems of medicine in the treatment of mental health disorders. *The Lancet Psychiatry, 2*(2), 168-177. doi:10.1016/s2215-0366(15)00013-9

Hackett, C., Grim, B. J., Cooperman, A., Ochoa, J. C., Gao, C., Shi, A. F., . . . Lugo, L. (2012). The Global Religious Landscape. A Report on the Size and Distribution of the World's Major Religious Groups as of 2010. *Pew Research Center*, 3-82. Retrieved from http://www.pewforum.org/global-religious-landscape.aspx

Haslbeck, J. M. B., & Waldorp, L. J. (2019). mgm: Estimating Time-Varying Mixed Graphical Models in High-Dimensional Data. *Journal of Statistical Software, VV*(II), 1-49.

Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2018). Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet*. doi:10.1016/s0140-6736(18)32408-5

Jeste, D. V., Palmer, B. W., Rettew, D. C., & Boardman, S. (2015). Positive psychiatry: its time has come. *J Clin Psychiatry, 76*(6), 675-683. doi:10.4088/JCP.14nr09599

Jeste, D. V., Savla, G. N., Thompson, W. K., Vahia, I. V., Glorioso, D. K., Martin, A. S., . . . Depp, C. A. (2013). Association between older age and more successful aging: critical role of resilience and depression. *Am J Psychiatry, 170*(2), 188-196. doi:10.1176/appi.ajp.2012.12030386

Kendler, K. S., Liu, X.-Q., Gardner, C. O., McCullough, M. E., Larson, D., & Prescott, C. A. (2003). Dimensions of Religiosity and Their Relationship to Lifetime Psychiatric and Substance Use Disorders. *American Journal of Psychiatry, 160*, 496-503.

Koenig, H. G., Hays, J. C., George, L. K., Blazer, D. G., Larson, D. B., & Landerman, L. R. (1997). Modeling the cross-sectional relationships between religion, physical health, social support, and depressive symptoms. *Am J Geriatr Psychiatry, 5*(2), 131-144.

Kudel, I., Cotton, S., Szaflarski, M., Holmes, W. C., & Tsevat, J. (2011). Spirituality and religiosity in patients with HIV: a test and expansion of a model. *Ann Behav Med, 41*(1), 92-103. doi:10.1007/s12160-010-9229-x

Lawrence, R. E., Oquendo, M. A., & Stanley, B. (2016). Religion and Suicide Risk: A Systematic Review. *Arch Suicide Res, 20*(1), 1-21. doi:10.1080/13811118.2015.1004494

Li, S., Okereke, O. I., Chang, S.-C., Kawachi, I., & VanderWeele, T. J. (2016). Religious Service Attendance and Lower Depression Among Women—a Prospective Cohort Study. *Annals of Behavioral Medicine, 50*(6), 876-884. doi:10.1007/s12160-016-9813-9

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2019). Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. *J Psychiatr Res*. doi:10.1016/j.jpsychires.2019.08.002

McElroy, E., Napoleone, E., Wolpert, M., & Patalay, P. (2019). Structure and Connectivity of Depressive Symptom Networks Corresponding to Early Treatment Response. *EClinicalMedicine, 8*, 29-36. doi:10.1016/j.eclinm.2019.02.009

Miller, L., Wickramaratne, P., Gameroff, M. J., Sage, M., Tenke, C. E., & Weissman, M. M. (2012). Religiosity and major depression in adults at high risk: a ten-year prospective study. *Am J Psychiatry, 169*(1), 89-94. doi:10.1176/appi.ajp.2011.10121823

Montgomery, B. E., Stewart, K. E., Bryant, K. J., & Ounpraseuth, S. T. (2014). Dimensions of religion, depression symptomatology, and substance use among rural African American cocaine users. *J Ethn Subst Abuse, 13*(1), 72-90. doi:10.1080/15332640.2014.873605

Mosqueiro, B. P., da Rocha, N. S., & Fleck, M. P. d. A. (2015). Intrinsic religiosity, resilience, quality of life, and suicide risk in depressed inpatients. *J Affect Disord, 179*, 128-133. doi:10.1016/j.jad.2015.03.022

Ostergaard, S. D., Jensen, S. O., & Bech, P. (2011). The heterogeneity of the depressive syndrome: when numbers get serious. *Acta Psychiatr Scand, 124*(6), 495-496. doi:10.1111/j.1600-0447.2011.01744.x

Panzini, R. G., Maganha, C., Rocha, N. S., Bandeira, D. R., & Fleck, M. P. (2011). Brazilian validation of the Quality of Life Instrument/spirituality, religion and personal beliefs. *Rev Saude Publica, 45*(1), 153-165.

Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., . . . Whiteford, H. (2016). Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *The Lancet, 387*(10028), 1672-1685. doi:10.1016/s0140-6736(15)00390-6

Scelzo, A., Di Somma, S., Antonini, P., Montross, L. P., Schork, N., Brenner, D., & Jeste, D. V. (2018). Mixed-methods quantitative-qualitative study of 29 nonagenarians and centenarians in rural Southern Italy: focus on positive psychological traits. *Int Psychogeriatr, 30*(1), 31-38. doi:10.1017/S1041610217002721

Schiavon, C. C., Marchetti, E., Gurgel, L. G., Busnello, F. M., & Reppold, C. T. (2016). Optimism and Hope in Chronic Disease: A Systematic Review. *Front Psychol, 7*, 2022. doi:10.3389/fpsyg.2016.02022

Smith, T. B., McCullough, M. E., & Poll, J. (2003). Religiousness and depression: Evidence for a main effect and the moderating influence of stressful life events. *Psychological Bulletin, 129*(4), 614-636. doi:10.1037/0033-2909.129.4.614

Southwick, S. M., & Charney, D. S. (2012). The science of resilience: implications for the prevention and treatment of depression. *Science, 338*(6103), 79-82. doi:10.1126/science.1222942

Souza, L. H., Salum, G. A., Mosqueiro, B. P., Caldieraro, M. A., Guerra, T. A., & Fleck, M. P. (2016). Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. *J Affect Disord, 193*, 373-380. doi:10.1016/j.jad.2016.01.004

Taunay, T. C. D., Gondim, F. d. A. A., Macedo, D. S., Moreira-Almeida, A., Gurgel, L. d. A., Andrade, L. M. S., & Carvalho, A. F. (2012). Validity of the Brazilian version of the Duke Religion Index (DUREL). *Rev Psiq. Clín., 39*, 130-135.

Thimm, J. C., Holte, A., Brennen, T., & Wang, C. E. (2013). Hope and expectancies for future events in depression. *Front Psychol, 4*, 470. doi:10.3389/fpsyg.2013.00470

Vaillant, G. E. (2013). Psychiatry, religion, positive emotions and spirituality. *Asian J Psychiatr, 6*(6), 590-594. doi:10.1016/j.ajp.2013.08.073

Van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B. W., Waldorp, L. J., & Schoevers, R. A. (2015). Association of Symptom Network Structure With the Course of Depression. *JAMA Psychiatry, 72*(12), 1219-1226. doi:10.1001/jamapsychiatry.2015.2079

van den Brink, R. H. S., Schutter, N., Hanssen, D. J. C., Elzinga, B. M., Rabeling-Keus, I. M., Stek, M. L., . . . Oude Voshaar, R. C. (2018). Prognostic significance of social network, social support and loneliness for course of major depressive disorder in adulthood and old age. *Epidemiol Psychiatr Sci, 27*(3), 266-277. doi:10.1017/S2045796017000014

Vance, T., Maes, H. H., & Kendler, K. S. (2014). A multivariate twin study of the dimensions of religiosity and common psychiatric and substance use disorders. *J Nerv Ment Dis, 202*(5), 360-367. doi:10.1097/NMD.0000000000000131

VanderWeele, T. J., Li, S., Tsai, A. C., & Kawachi, I. (2016). Association Between Religious Service Attendance and Lower Suicide Rates Among US Women. *JAMA Psychiatry, 73*(8), 845-851. doi:10.1001/jamapsychiatry.2016.1243

VanderWeele, T. J., McNeely, E., & Koh, H. K. (2019). Reimagining Health-Flourishing. *JAMA, 321*(17), 1667-1668. doi:10.1001/jama.2019.3035

Vares, E. A., Salum, G. A., Spanemberg, L., Caldieraro, M. A., & Fleck, M. P. (2015). Depression Dimensions: Integrating Clinical Signs and Symptoms from the Perspectives of Clinicians and Patients. *PLoS One, 10*(8),

Wagnild, G. M. (2014). *The Resilience Scale User's Guide* (P. E. Guinn Ed.). Montana, United States of America: Resilience Center.

World-Health-Organization. (2014). Preventing suicide: A global imperative.

Figure Legends

Table 1. Sociodemographic and clinical variables of depressed patients (N=153)

	Frequency	%
Female	116	76.3
Male	36	23.7
White	132	86.8
Non-white	19	12.5
Single	19	12.5
Married	76	50.0
Divorced	37	24.3
Widowed	20	13.2
Employed	23	15.1
Unemployed	40	26.3
Stay at home	17	11.2
Student	8	2.0
Retired	18	11.8
Health insurance	51	33.5
Familiar history of suicide	36	23.5
Previous suicide attempt	65	42.5
Psychiatric comorbidities		
Melancholic features	89	58.2
Previous hypomania	14	9.2
Previous mania	16	10.5
Current psychosis	33	21.6
Previous psychosis	64	41.8
Panic disorder	23	15.0
Social phobia	32	20.9
Obsessive compulsive disorder	26	17.0
Post-traumatic stress disorder	12	7.8
Generalized anxiety disorder	71	46.4

	Mean	SD
Age	51.2	11.3
Education (years of study)	8.63	3.96
Age of depression onset	32.6	15.3
Number of depressive episodes	3.33	2.51
Years since first depressive episode	18.6	13.5
Clinical Global Impression	4.86	0.90
Social Support (MOS)	64.9	18.4
Resilience (RS-14)	55.6	14.5
Depressive symptoms (HAM-D)	21.9	4.95

Table 2. Religious demographic characteristics of depressed patients (N=153)

Religion Affiliation	**Frequency**	**%**
Catholic	62	40.8
Evangelical religions	24	15.8
Spiritism	26	17.1
Afro-Brazilian religions	4	2.6
Spiritual but not religious	25	16.4
Agnosticism	2	1.3
Atheism	3	2.0
Religious Attendance		
More than once a week	29	19.0
Once a week	29	19.0
A few times a month	42	27.5
A few times a year	21	13.7
Once a year or less	20	13.1
Never	12	7.8
Private Practices		
More than once a week	32	20.9
Once a week	10	6.5
A few times a month	6	3.5
A few times a year	20	14.2
Once a year or less	59	36.3
Never	26	19.5
Intrinsic Religiosity		
High IR (≥10)	98	64.1

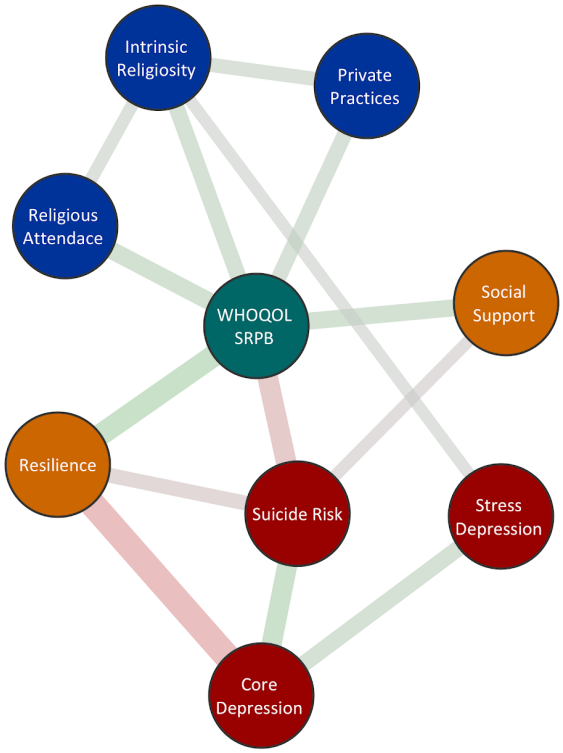

Figure 1. Network analysis (MGM R-package; Cytoscape). Green edges indicate positive relationships and red edges indicate negative relationships. Thicker edges indicate stronger connections between nodes. Network analysis nodes include religious attendance, private practices, intrinsic religiosity (DUREL), WHOQOL SRPB, resilience (RS-14), social support (MOS-SSS), depressive symptoms domains of HAM-D, core depressive symptoms (HAM-D-6: 1, 2, 7, 8, 10, and 13), stress-arousal depression symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16) and suicide risk (HAM-D-2: 3 and 17).

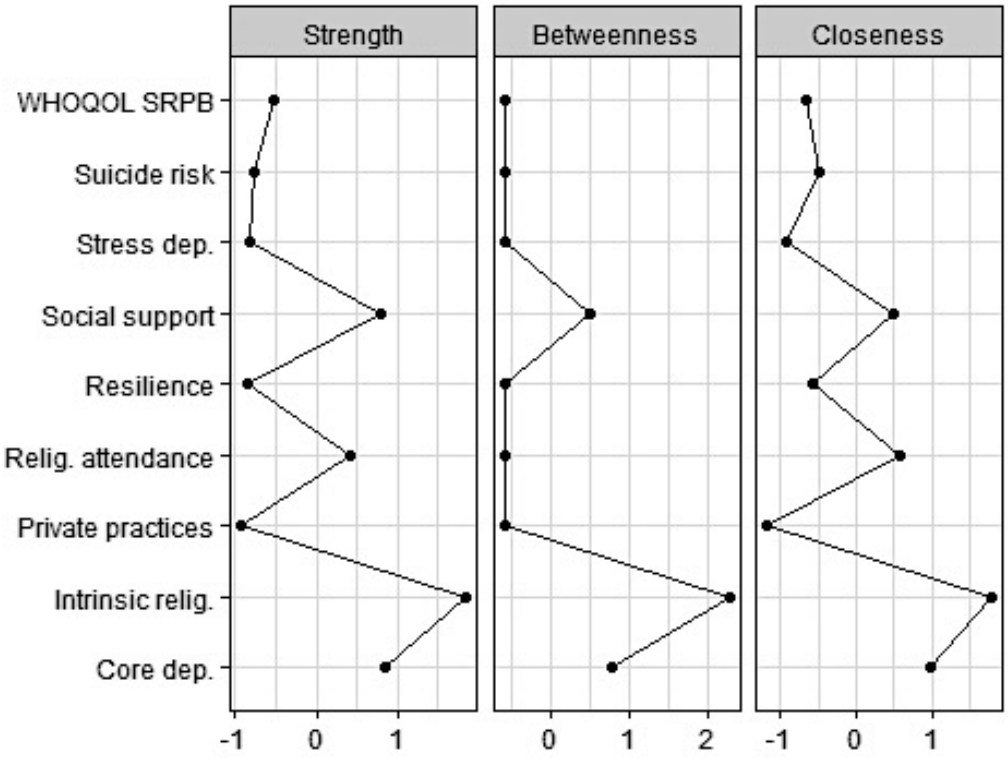

Figure 2. Centrality measures for network 1. Network analysis nodes include religious attendance, private practices, intrinsic religiosity (DUREL), WHOQOL SRPB total score, resilience (RS-14), social support (MOS-SSS), and depressive symptoms domains of HAM-D, core depressive symptoms (HAM-D-6: 1, 2, 7, 8, 10, and 13) and stress-arousal depression symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16) and suicide risk (HAM-D-2: 3 and 17).

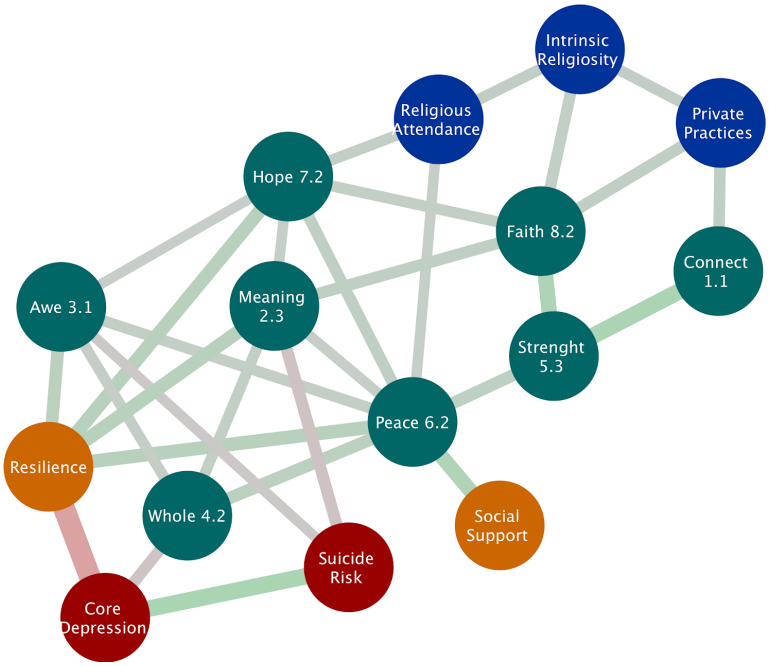

Figure 3. Network model 2 (MGM R-package; Cytoscape). Green edges indicate positive relationships and red edges indicate negative relationships. Thicker edges indicate stronger connections between nodes. Network analysis nodes include religious attendance, private practices, intrinsic religiosity (DUREL), WHOQOL SRPB items of connect, meaning, awe, strength, whole, peace, hope, and faith, resilience (RS-14), social support (MOS-SSS), depressive symptoms domains of HAM-D, core depressive symptoms (HAM-D-6: 1, 2, 7, 8, 10, and 13), and stress-arousal depression symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16) and suicide risk (HAM-D-2: 3 and 17).

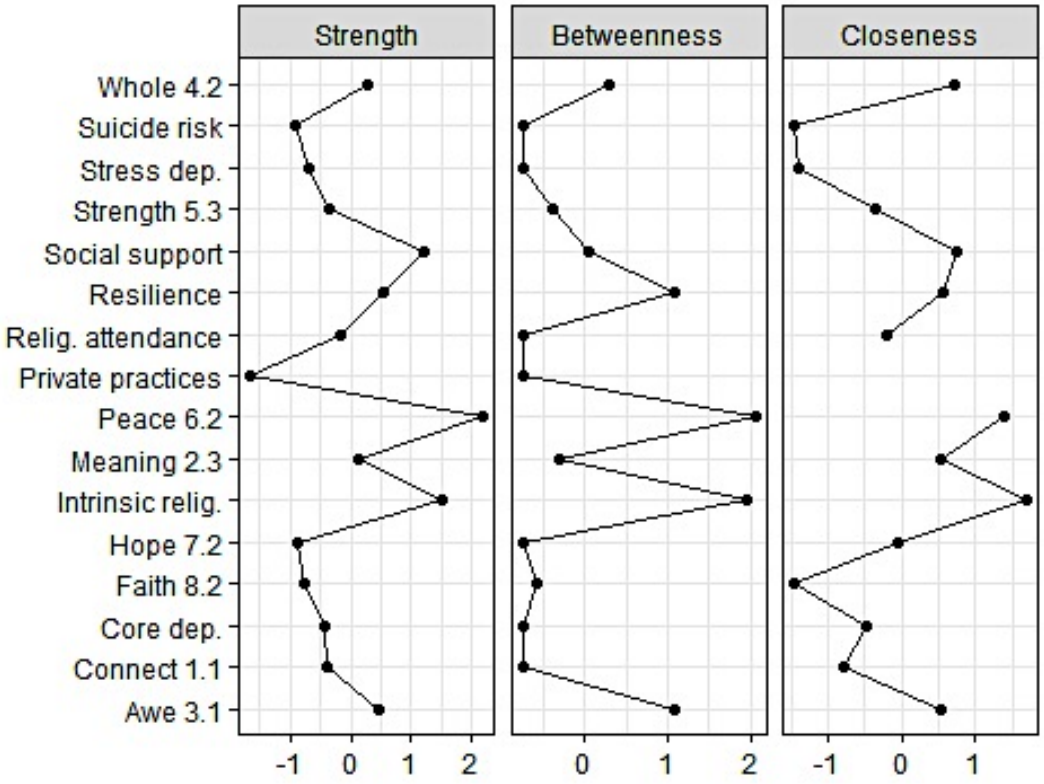

Figure 4. Centrality measures for network 2. Network analysis nodes include religious attendance, private practices, intrinsic religiosity (DUREL), WHOQOL SRPB items of connect, meaning, awe, strength, whole, peace, hope, and faith, resilience (RS-14), social support (MOS-SSS), depressive symptoms domains of HAM-D, core depressive symptoms (HAM-D-6: 1, 2, 7, 8, 10, and 13), stress-arousal depression symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16), and suicide risk (HAM-D-2: 3 and 17).

Supplementary Materials

Table S1. Correlation stability analysis (mgm)*

	N Person	Drop %	n
1	36	74.8	95
2	47	67.1	105
3	58	59.4	123
4	69	51.7	70
5	80	44.1	89
6	91	36.4	111
7	102	28.7	93
8	114	20.3	113
9	125	12.6	90
10	136	4.9	111

*Maximum drop proportions to retain correlation of 0.7 in at least 95% of the samples: edge: 0.517; strength: 0.517.

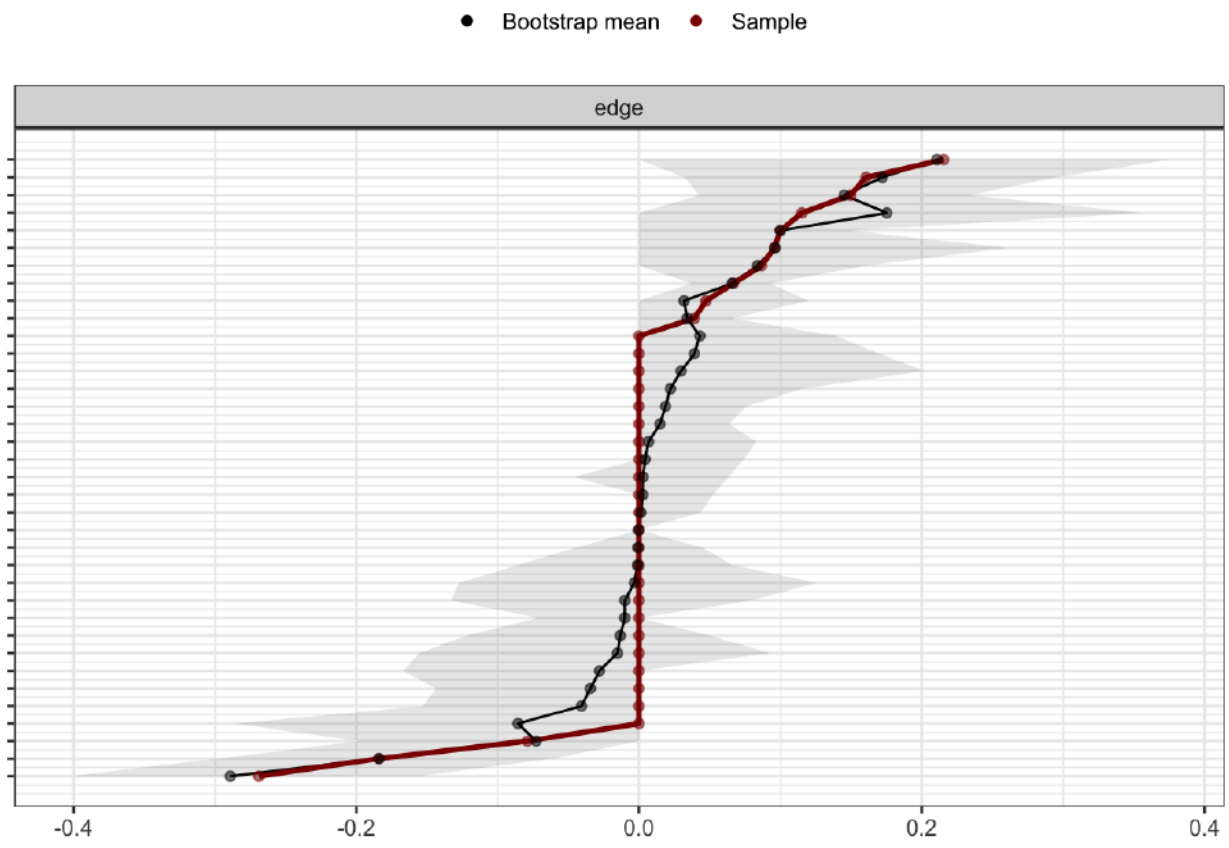

Figure S1. Bootstrapping results for network 1. Confidence intervals of estimated edge-weights for the network of religious attendance, private practices, intrinsic religiosity (DUREL), WHOQOL SRPB total score, resilience (RS-14), social support (MOS-SSS), and HAM-D core depressive symptoms (HAM-D-6: 1, 2, 7, 8, 10, and 13), stress-arousal depression symptomatology (HAM-D-9: 4, 5, 6, 9, 11, 12, 14, 15, and 16), and suicide risk (HAM-D-2: 3 and 17). Sample values are indicated by the red line and the bootstrapped confidence intervals by the gray area. Each horizontal line represents one edge of the network, ordered from the edge with the highest weight to the edge with the lowest weight. The mean of the bootstrap samples is represented by the dark ties. The y-axis labels have been removed to avoid cluttering.

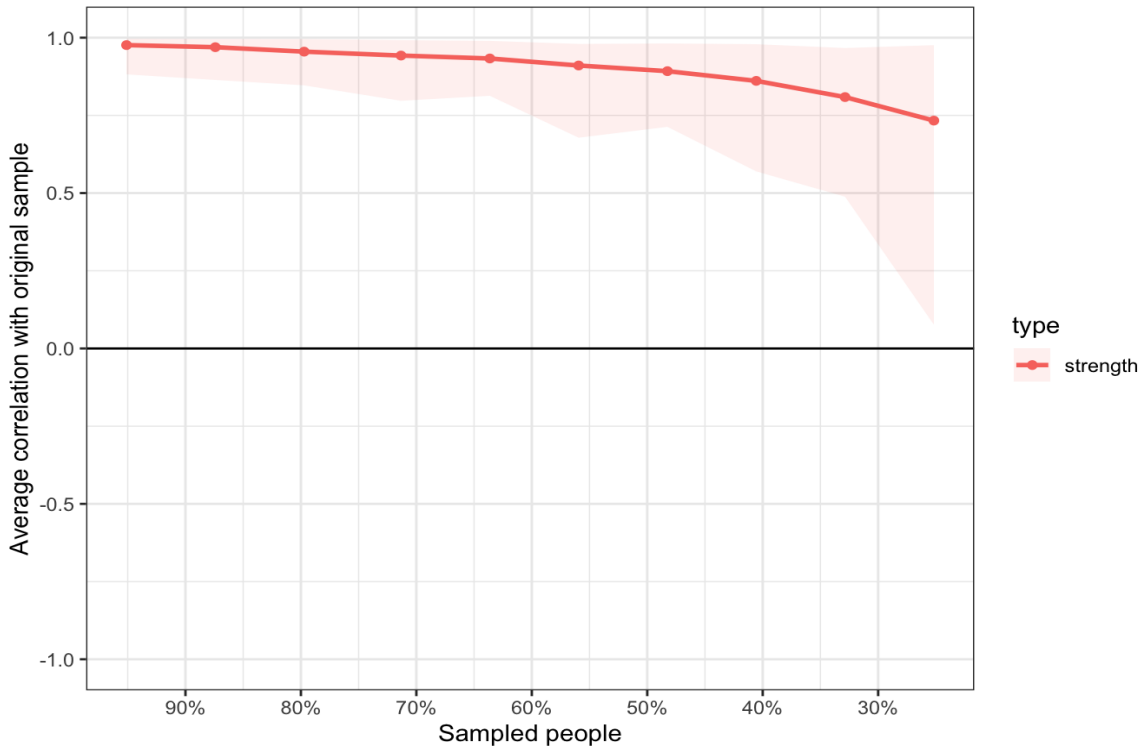

Figure S2. Stability of centrality for network 1.

9. ARTIGO #3

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Religiosity, spirituality, suicide risk and remission of depressive symptoms: a 6-month prospective study of tertiary care Brazilian patients

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Abstract

Religiosity and spirituality (R/S) are increasingly recognized as significant aspects in the evaluation of depressed patients. Limited research, however, has investigated the impact of R/S on outcomes of more severe or chronic depressed patients. The present study investigated the impact different religiosity dimensions in tertiary care Brazilian depressed patients over suicide risk scores measured at baseline and remission of depressive symptoms in a 6-month prospective follow-up. In 277 individuals interviewed, 226 presented a diagnosis of depressive episode and 192 where assessed in the follow-up. Religiosity was evaluated using the Duke University Religion Index, comprising three dimensions of religiosity (organizational religiosity, non-organizational religiosity, intrinsic religiosity). Other potential predictors of outcomes included the Childhood Trauma Questionnaire (CTQ), Maudsley Staging of illness (MSM), Medical Outcomes Study Social Support Survey (MOS), World Health Organization Spirituality, Religiousness and Personal Beliefs instrument (WHOQOL-SRPB) and Hamilton Depression Scale (HAM-D). Results showed that almost half (46.1%) of the patients reported previous suicide attempts. Linear regression models identified that religious attendance (t-statistic -2.172, P=0.03), intrinsic religiosity (t-statistic -2.421, P=0.01) and WHOQOL-SRPB (t-statistic -3.670, P=0.00) were inversely correlated to suicide risk scores. In a prospective follow-up 16.7 % of patients (n=32/192) achieved remission of depressive symptoms (HAM-D scores ≤7). Religious attendance (OR 1.83, P=0.02) was identified as the main predictor of remission. Findings reinforce the importance of attending to religiosity/spirituality in order to improve outcomes and promote the recovery especially among severely depressed patients with increased suicide risk.

Keywords

Religiosity, Spirituality, Depression, Suicide, Remission, Social Support

Introduction

Depression is a chronic and recurrent disorder with serious impacts on mental health (Herrman et al., 2018). Large prospective cohort studies report that only 17% of patients achieve recovery of depression in a 6-year follow up, with most patients presenting a chronic and disabling course, 67.8% experiencing recurrent episodes and 14.7% manifesting consistently chronic symptomatology (Verduijn et al., 2017). The likelihood of recovery markedly decreases over time in patients with severe or chronic depressive episodes (Keller et al., 1992). Furthermore, suicide represents a serious concern among those patients, with estimated 10 times higher suicide rates compared to the general population (Bachmann, 2018; Fazel & Runeson, 2020). Tertiary care depressed patients experience an even worse course of illness, with higher suicide risk, multiple psychiatric comorbidities, and higher rates of exposure to childhood trauma and neglect (Caldieraro et al., 2013; Paterniti, Sterner, Caldwell, & Bisserbe, 2017; Vares et al., 2015).

Religiosity and spirituality are increasingly recognized as significant aspects in the evaluation of depressed patients (Miller et al., 2012). Many people turn to religion as a coping resource to deal with depressive symptoms (K. I. Pargament & Lomax, 2013). Religious social support provided by community members also offers many patients a relevant resource in the face of suffering and distress (Gureje et al., 2015). Furthermore, evidence demonstrates that different dimensions of religiosity/spirituality (R/S) are prospectively associated with a better course of depression (Braam & Koenig, 2019). Some dimensions of religious involvement, such as intrinsic religiosity, have been associated with faster remission of depressive symptoms among elderly outpatients, lower suicide risk and better outcomes among depressed inpatients (Harold G. Koenig et al., 1998; Bruno Paz Mosqueiro et al., 2015). Religious attendance has been associated with fewer depressive symptoms and is a strong protective factor against suicide (S. Li et al., 2016; VanderWeele et al., 2016). Limited research, however, has investigated the impact of R/S on outcomes of more severe or chronic depressed patients (Braam & Koenig, 2019).

The majority of the world's population (84% or 6.9 billion people) reports affiliation with religious institutions (Hackett et al., 2012). Particularly in Brazil, most people (83.8%) identify religion as a very important domain of their lives (Moreira-Almeida et al., 2010). Nevertheless, it has been estimated that around three quarters of research regarding R/S and health has been performed in Western countries (most in North America and Europe) and predominantly with Christian populations (H. G. Koenig et al., 2012). A recent systematic review, for instance, identified only one prospective study evaluating the impact of R/S on depression outcomes in Latin America (Braam & Koenig, 2019). Considering that, there is a clear need for more R/S research in different cultures and religious backgrounds (Braam et al., 2010).

The present study evaluated the impact of three dimensions of religiosity in tertiary care Brazilian depressed patients with respect to two main outcomes: (1) a suicide risk score

measured at baseline assessment; and (2) remission rates of depressive symptoms in a 6-month prospective follow-up. The effects of R/S were controlled for different clinical variables, including severity of depressive symptoms, staging of illness, childhood traumatic experiences and social support.

Materials and Methods

Participants and Treatment Setting

The present study evaluated patients with a diagnosis of depressive episode in the mood disorder outpatient clinic at Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care university hospital in Brazil. The mood disorder outpatient clinic provides specialized treatment for individuals with chronic, refractory or severe depressive symptomatology referred by primary care settings and other medical specialties at HCPA. The treatment of depression follows standard international guidelines and best available evidence-based practices for management of depression, adapted to psychiatric medications available at Brazilian public health system (Fleck et al., 2009; Kennedy et al., 2016; Yatham et al., 2018). Structured clinical consultations are scheduled every 2 to 4 weeks to evaluate the response to pharmacotherapy as well as the emergence of side effects. Outcomes are routinely monitored using measurement-based care. The approach to treatment resistant depression involves a careful and comprehensive psychosocial assessment and stepwise clinical strategies, including optimizing antidepressant doses, switching of antidepressants, use of adjunctive medications (e.g. lithium, tricyclic antidepressants, bupropion, atypical antipsychotics) and for more chronic resistant depression, electroconvulsive therapy or monoamine oxidase inhibitors (MAOIs).

In 277 individuals interviewed from 2014 to 2018, 226 subjects presented a diagnosis of depressive episode and where included in the study (flowchart Figure 1). Written informed consent was obtained according to the approval provided by the hospital ethical committee. Patients with severe clinical comorbidities or individuals with significant cognitive deficits that limited comprehension of self-report instruments and individuals with acute manic or hypomanic episodes were not included in the study.

From the baseline sample, 157 patients were prospectively evaluated in a 6-month scheduled follow-up. Of the 69 patients who missed the scheduled interview, HAM-D scores for 34 patients were retrieved from hospital records in their last observation. The total sample considered for statistical analysis in the follow-up comprised 192 patients.

Assessments

Depressive Symptoms and Suicide Risk

The diagnosis of depressive episode and psychiatric comorbidities was performed using the Brazilian Portuguese version of Mini International Neuropsychiatric Interview (MINI-Plus) (Amorim, 2000). Depressive symptoms were assessed at baseline and follow-up by the Brazilian Portuguese validated version of 17-item Hamilton Depression Rating Scale

(HAM-D) (Hamilton, 1967). The HAM-D scores at follow-up were used to define depressive symptom remission (HAM-D ≤7). Suicide risk scores were retrieved from MINI-Plus (C1-C6 items). A continuous score of suicide risk was defined by the sum of the six items ranging from 0 to 33 points, with greater scores reflecting higher suicide risk (Amorim, 2000). The Maudsley staging method (MSM) was used to evaluate the severity of depression course and treatment resistant-depression (Fekadu, Donocik, & Cleare, 2018). The instrument comprises 5 questions quantifying the duration and severity of current depressive episode, number of previous treatment failures, use of augmentation strategies and electroconvulsive therapy. Higher MSM scores predict a more severe course of illness and worse treatment outcomes.

Childhood Traumatic Experiences

The Childhood Trauma Questionnaire (CTQ) Brazilian validated version was used for assessment of childhood abuse and neglect experiences (Grassi-Oliveira et al., 2014). The instrument is composed by 28 Likert-scale questions. The results of multilinear regression models analysis were classified into two broad categories with continuous scores of childhood abuse experiences (encompassing emotional, physical and sexual abuse) and childhood neglect experiences (emotional and physical neglect).

Religiosity

Religiosity was assessed using the Brazilian-Portuguese validated version of Duke University Religion Index (DUREL) (Taunay et al., 2012). The instrument consists of 5 Likert-scale questions, comprising three dimensions of religiosity. The first question evaluates the frequency of religious attendance (organizational religiosity), the second the frequency of private religious practices (such as prayer, meditation or religious reading -non-organizational religiosity) and the last three questions cover intrinsic religiosity (the degree of personal religious faith and commitment to religious beliefs in life).

Spirituality

The 8-item version of World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs instrument (WHOQOL-SRPB) was used to evaluate characteristics related to spirituality and quality of life (Zimpel et al., 2019). The instrument is composed of 6 domains that provide a an overall score, including measures of connection (*extent that any connection to a spiritual being helps through hard times*), meaning (*extent that life has a purpose*), awe (*experiences of awe from surroundings such as art, nature, music*), wholeness (*balance between mind, body and soul*), strength (*extent that spiritual strength helps one to live better*), peace (*extent of inner peace*), hope (*extent that an individual is hopeful about life*), faith (*extent that faith gives comfort in daily life*).

Social Support

Social support was assessed with the Brazilian validated version of the Medical Outcomes Study Social Support Survey (MOS), a 28-item Likert scale, with scores ranging from 5 to 140 points (Griep, Chor, Faerstein, Werneck, & Lopes, 2005). Higher scores indicate a greater perception of social support. The instrument evaluates an individual's perceived availability of different functional aspects of support, including emotional support (availability of people expressing positive affect, empathetic understanding, encouragement), informational support (availability of people offering advice, information, guidance or feedback), material support (people available to provide material or behavioral assistance), positive social interaction (availability of people to fun or recreation), and affectionate support (availability of people who express care and affection).

Statistical Analysis

Descriptive analysis provided an overview of sample clinical and socio-demographic characteristics. Data are presented as means ± standard deviations or percentages unless specified otherwise.

Multilinear regression models were used to test for the effects of different R/S domains on suicide risk continuous scores at baseline. Considering the high collinearity between R/S dimensions, each dimension was individually tested as an independent predictor for the multilinear regression models. The R/S domains included in analysis were (1) religious attendance (DUREL), (2) private religious practices (DUREL), (3) intrinsic religiosity (DUREL) and (4) WHOQOL-SRPB (total score). Other independent variables included in the multilinear regression models, selected according to literature as relevant predictors of suicide risk in tertiary care depressed patients, were socio-demographic factors (age, sex), early developmental factors (CTQ continuous scores of childhood trauma and neglect) and variables related to the present episode and condition (HAM-D severity of depressive symptoms at baseline and social support).

In a second step, a logistic regression model evaluated the impact of religiosity dimensions (DUREL) and WHOQOL-SRPB (total score) on the odds of remission of depressive symptoms in a 6 month-follow up. Relevant variables related to R/S and potentially confounders of depressive symptoms were included in the model, including social support (MOS), childhood trauma (CTQ) and neglect (CTQ) and Maudsley staging of illness (MSM). Diverse dimensions of MSM were included in the model to understand their impact on the odds of remission of depressive symptoms (e.g. duration of illness, severity, treatment failure and use of augmentation strategies). The limited number of patients who underwent

ECT limited the inclusion of the last MSM dimension in the model. For all analyses, statistically significant results were defined as a $P<0.05$.

Results

Depressive Symptoms, Childhood Traumatic Experiences and Baseline Characteristics

Study participants were mainly women (78.2%), white (84.9%), middle-aged (mean 51.0±11.2 years), with most unable to attend work (35.1%) or unemployed (23.1%). Most participants reported mean moderate to severe depressive symptoms at baseline (mean HAM-D = 21.5±5.54), with a long trajectory of lifetime depressive symptoms (mean 18.1±13.8 years since the first episode), and multiple depressive episodes (3.52±2.79). Diverse psychiatric features and comorbidities were identified by the psychiatric interview (MINI) along with a diagnosis of depressive episode, the most common being melancholic characteristics (55.3%), generalized anxiety disorder (45.7%), previous psychosis (37.8%) and social phobia (20.5%) (Table 1). The Maudsley staging instrument (MSM) revealed mean moderate to severe scores, indicating a poor course and potential treatment-resistant depression (mean MSM 8.6, SD 1.7).

Adding to that, almost half (46.1%) of the patients reported previous suicide attempts and a quarter a family history of suicide (24.1%). The reported prevalence of moderate to severe experiences of childhood trauma according to the different categories assessed by the CTQ were: neglect: 9.3%, physical abuse: 9.7%, sexual abuse: 9.8%, and emotional abuse: 16.4%.

Predictors of Suicide Risk

Linear regression models evaluated the effect of R/S dimensions and social support on suicide risk scores at baseline. Results indicated that religious attendance (t-statistic -2.172, P=0.03), intrinsic religiosity (t-statistic -2.421, P=0.01) and WHOQOL-SRPB total score (t-statistic -3.670, P=0.00) were statistically significantly inversely correlated to suicide risk (Table 3). Depressive symptoms at baseline were directly correlated to suicide risk in all regression models. Age, sex, private religious practices, and social support otherwise did not present statistically significant associations with suicide risk in multilinear regression models (Table 3).

Response and Remission

In a prospective follow up, 25.2% of patients (n=57/192) responded to treatments (improvements in depressive symptoms ≥ 50% in HAM-D scores) and 16.7 % of patients (n=32/192) achieved remission of depressive symptoms (HAM-D scores ≤7). The mean time of observation of the patients who missed the scheduled follow-up interview (n=39) was 2.6 months (SD 1.6). For those patients, HAM-D scores were retrieved from hospital records in their last observation carried forward in previous consultations. The mean HAM-D scores for

those patients were quite similar to that of those patients who attended the 6-month interview (15.2 vs. 15.0, respectively, view Table 1).

Predictors of Remission

Table 3 describes the predictors of remission of depressive symptoms in the prospective follow-up. Religious attendance (DUREL) was the main predictor of remission of depressive symptoms (OR 1.83, P=0.02). Social support (MOS), then, was also identified as a significant predictor of remission (OR 1.03, P=0.02). Other socio-demographic and clinical variables were not significant predictors of remission of depressive symptoms, including age, sex, childhood experiences of trauma and neglect (CTQ), staging of illness domains (MSM) and other R/S dimensions (private practices, intrinsic religiosity and WHOQOL-SRPB) (Table 3, figure 2).

Discussion

This study found that different R/S dimensions were correlated with relevant outcomes among tertiary care Brazilian depressed patients. Religious attendance, intrinsic religiosity and WHOQOL-SRPB scores were inversely correlated with suicide risk scores at baseline. Furthermore, religious attendance was identified as the main predictor of remission in a 6-month follow-up of depressed individuals.

The correlation of R/S dimensions with suicide risk is particularly relevant in a tertiary care depressed patient sample with elevated suicide risk. This finding is consistent with other evidence supporting the role of religiosity generally as protective factor to suicide (Fazel & Runeson, 2020). A study of Brazilian psychiatric patients with bipolar disorder found non-organized religious practices and intrinsic religiosity to be inversely associated with suicidal behavior (Caribe et al., 2015). A systematic review of 89 studies also reported that religious affiliation and religious service attendance were significant protective factors of suicide attempts across different countries worldwide (Lawrence et al., 2016). A recent large prospective cohort study of US women (n=89,708) found that frequent religious attendance reduced by 5 times the odds of completed suicide (VanderWeele et al., 2016).

It is of interest that the impact of religious attendance on remission of depressive symptoms in our study persisted after controlling for the potentially confounding effects of social support and stage of depression. Other empirical work has established that religiosity is mainly a protective factor against incident depression (Miller et al., 2012) and for recovery from depressive episodes (Harold G. Koenig et al., 1998). Religious attendance, specifically, has been demonstrated to be a predictor of better outcomes among depressed patients (Braam & Koenig, 2019). A large prospective cohort study of 48,984 women in United States found that women with higher religious service attendance had the lowest risk for development of depression (OR 0.71) compared to those women who never attended religious groups (S. Li et al., 2016). The protective effects of religious attendance on depressive symptoms might be explained by multiple factors, including the use of religious-based coping strategies, a worship-based sense of meaning, coherence and belonging, religiously motivated positive mental attitudes (e.g. forgiveness, gratitude, hope, optimism) and encouragement of healthy behaviors (e.g. volunteering, lower alcohol consumption or smoking) (Krause, Hill, Emmons, Pargament, & Ironson, 2016; Moreira-Almeida, Neto, & Koenig, 2006; VanderWeele, Balboni, & Koh, 2017).

Social support was also independently a significant predictor of remission of depressive symptoms in our study. Extant recent literature in that regard reinforces the relevance of perceived social support to recovery among depressed patients (Leskela et al., 2006). For instance, loneliness has been associated with more severe depressive symptoms

and lower remission in 2-year prospective follow-up of patients with late-life depression (Holvast et al., 2015). Similarly, a recent study of 1474 depressed patients in the Netherlands reported that different aspects of social support (e.g. living a large household, negative social relationships and loneliness) were related to the course of depression (Van den Brink et al., 2018). Adding to that, improving interpersonal relationships and social support represent a key element of interpersonal psychotherapy interventions for depression (Souza et al., 2016).

The present study showed that 16 % of patients achieved remission of depressive symptoms in a 6-month follow-up. Different prospective studies in clinical outpatient settings report remission rates of depression that vary from 50% in 6-months (Keller, 1992) to 3.6% in a year for patients with treatment-resistant depression (Dunner et al., 2006). Despite that, chronic depressed patients often need more time to achieve recovery. The likelihood of remission decreases with multiple episodes in what has been called treatment-resistant depression (Richards, 2011). According to the STAR-D study, remission of depressive symptoms with pharmacological treatments is more likely to occur during the first trials (around 20-30%) and significantly decreases with multiple attempts (10-20%) (Gaynes et al., 2009). In agreement with our findings, a recent prospective study reports a less successful long-term course of depressed patients, with only 41% to 32% of remission rates at 4 and 6 years of follow-up, and up to 34% of patients experiencing chronic episodes lasting more than 2 years (Verduijn et al., 2017).

Notably, other potentially relevant variables were not predictors of outcomes in the present sample, including childhood traumatic experiences and course of illness staging. These findings might suggest that in a middle age sample of persistently depressed patients, variables related to the current episode (e.g. spirituality, religious involvement and social support) play a more significant role in achieving improvement of depressive symptoms compared to trajectory of illness or lifetime variables (childhood traumatic experiences and depressive staging). Nevertheless, a few caveats should be considered. First, the whole sample reported lower mean scores of childhood trauma and neglect. Second, the retrospective evaluation of childhood experiences in a single evaluation among middle age patients could be subject to bias due to underreporting such traumatic experiences (Brietzke et al., 2012). Marked social vulnerabilities of this specific Brazilian sample would partially explain the predominant effect of psychosocial variables over clinical ones in depression outcomes (Bosworth, Park, McQuoid, Hays, & Steffens, 2003). Otherwise, our findings accord with life-course models for suicide risk, suggesting that different risk factors come into play in different stages of life (Fazel & Runeson, 2020). Based on this model, for middle-age patients recent life experiences (religious resources and social support) and characteristics related to the present episode (depression severity) would have more impact as compared with past childhood experiences.

The fact that religious attendance and intrinsic religiosity, but not private religious practices correlated with improvement raises the question whether engaging in such practices alone or without strong personal conviction is clinically meaningful (Harold G. Koenig, Peteet, et al., 2020). This is of interest in light of the widespread recommendation of spiritual practices such as mindfulness, and suggests a need for further qualitative (as well as quantitative) research into the role of R/S in recovery from depression. This study was subject to some limitations. First, patients were followed using a naturalistic design without controlling for the treatment received. Second, prospective studies of naturalistic samples suffer from missing data, though in our study this did not seem to influence results. Nevertheless, the present findings in a population of patients with major psychiatric and social vulnerabilities, including high suicide risk and treatment resistance are quite meaningful in reinforcing previous findings reporting the benefits of R/S and social support for recovery from depression, particularly in a country demonstrating special interest in R/S (Moreira-Almeida et al., 2010).

Conclusions

Different religious dimensions inversely correlated with suicide risk at baseline evaluation in a population of tertiary care, severely depressed Brazilian patients. Furthermore, religious attendance and social support were found to be the main predictors of remission at in a 6-month follow-up. These findings reinforce the importance of attending to religiosity/spirituality in order to improve outcomes and promote the recovery of severely depressed patients.

Figure 1.

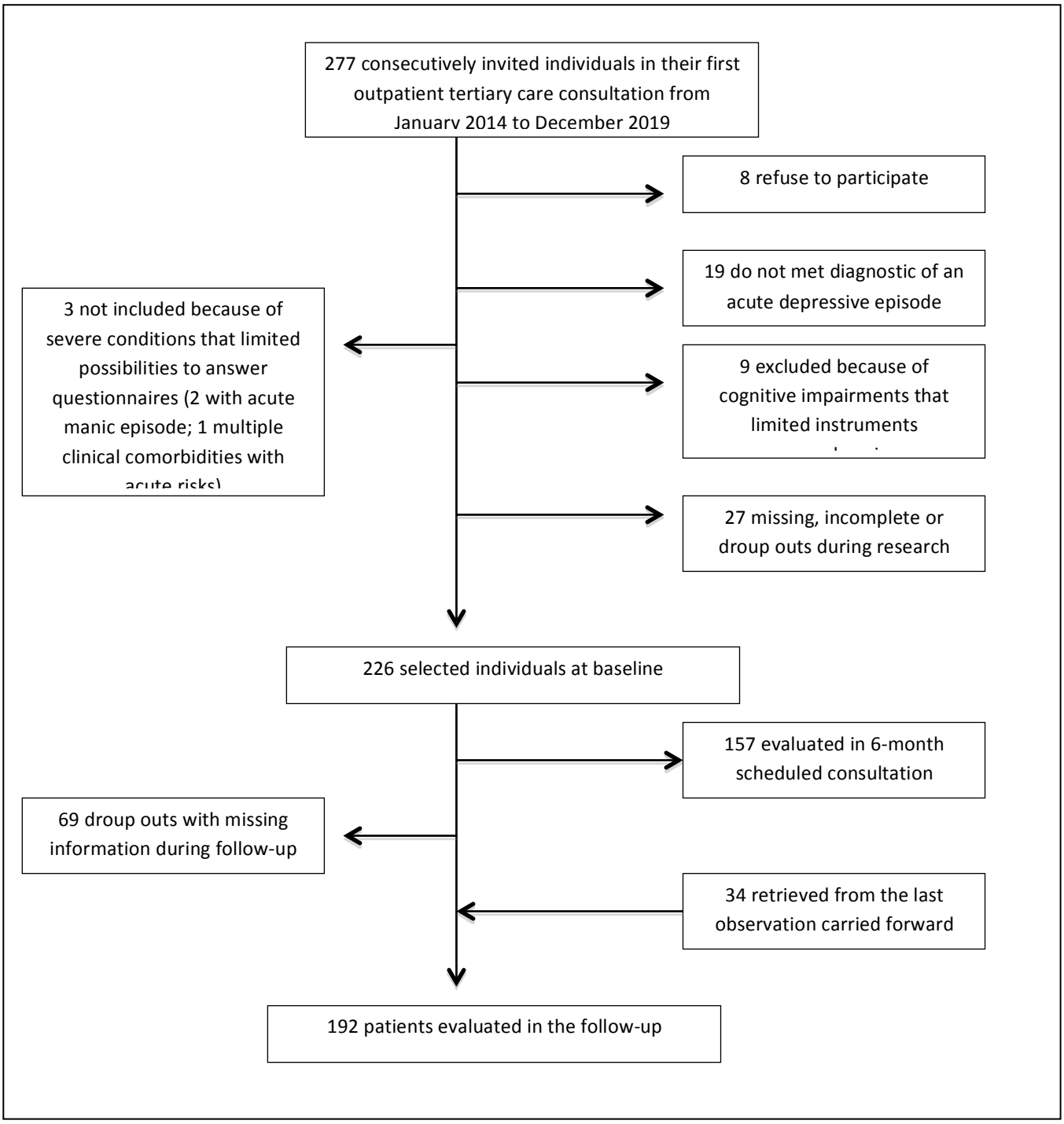

Figure 1.lowchart of depressed patient's inclusion and follow-up

Table 1.

Table 1. Socio-Demographic and Clinical Variables of Depressed Patients (n=226)

	Freq.	Perc. (%)
Female	176	78.2
Male	49	21.8
White	191	84.9
Non-White	34	15.1
Single	24	10.7
Married	119	52.9
Divorced	56	24.9
Widowed	26	11.6
Employed	40	17.8
Unemployed	52	23.1
Stay at home	25	11.1
Student	3	1.3
Retired	15	11.6
Health insurance	79	35.1
Familiar History of Suicide	56	24.7
Previous Suicide Attempt	104	46.0
Psychiatric Comorbidities		
Melancholic Features	125	55.3
Previous Hypomania	17	7.6
Previous Mania	20	8.9
Current Psychosis	45	20.0
Previous Psychosis	85	37.8
Panic Disorder	30	13.7
Social Phobia	45	20.5
OCD	33	15.1
PTSD	15	6.8
GAD	100	45.7

	Mean	(SD)
Age	51.0	11.2
Education (years study)	8.32	3.97
Age of Onset Depression	33.0	14.9
Number of Depressive Episodes	3.52	2.79
Years Since the First Episode	18.1	13.8
Maudsley (MSM global score)	8.6	1.7
Childhood Physical Abuse (CTQ)	3.8	4.4
Childhood Emotional Abuse (CTQ)	6.7	5.5
Childhood Sexual Abuse (CTQ)	2.0	4.2
Childhood Emotional Neglect (CTQ)	8.6	4.4
Childhood Physical Neglect (CTQ)	4.1	4.1
Social Support (MOS)	64.8	18.3

Depressive symptoms (HAM-D)	21.5	5.54
Depressive symptoms 6-month follow-up (HAM-D)	15.0	7.1
Depressive symptoms last observation carried forward (HAM-D)	15.2	7.2

Table 2

Table 2. Multilinear regression models of religiosity dimensions and suicide risk among depressed patients (N=135)

Predictors	**Suicide Risk**			
				Adjusted R-Square
Model 1	**Beta**	**t**	**Sig.**	(0.18, P=0.00)
Age	-0.147	-1.836	0.06	
Female	-0.083	-1.058	0.29	
Childhood Trauma (CTQ)	0.151	1.282	0.20	
Childhood Neglect (CTQ)	-0.058	-0.489	0.62	
Social Support (MOS)	0.007	0.085	0.93	
Depressive symptoms (HAM-D)	0.393	4.965	**0.00**	
Religious Attendance (DUREL)	-0.173	-2.172	**0.03**	
				Adjusted R-Square
Model 2	**Beta**	**t**	**Sig.**	(0.18, P=0.00)
Age	-0.128	-1.520	0.13	
Female	-0.076	-0.953	0.34	
Childhood Trauma (CTQ)	-0.134	1.136	0.25	
Childhood Neglect (CTQ)	-0.054	0.023	0.65	
Social Support (MOS)	0.023	0.279	0.78	
Depressive symptoms (HAM-D)	0.393	4.914	**0.00**	
Private Practices (DUREL)	-0.142	-1.656	0.10	
				Adjusted R-Square
Model 3	**Beta**	**t**	**Sig.**	(0.20, P=0.00)
Age	-0.117	-1.418	0.15	
Female	-0.043	-0.540	0.59	
Childhood Trauma (CTQ)	0.148	1.264	0.20	
Childhood Neglect (CTQ)	-0.053	-0.451	0.65	
Social Support (MOS)	0.024	0.290	0.77	
Depressive symptoms (HAM-D)	0.388	4.933	**0.00**	
Intrinsic Religiosity (DUREL)	-0.202	-2.421	**0.01**	
				Adjusted R-Square
Model 4	**Beta**	**t**	**Sig.**	(0.24, P=0.000)
Age	-0.102	-1.237	0.21	
Female	-0.048	-0.616	0.53	
Childhood Trauma (CTQ)	0.085	0.749	0.45	
Childhood Neglect (CTQ)	-0.001	-0.007	0.53	
Social Support (MOS)	0.084	1.007	0.99	
Depressive symptoms (HAM-D)	0.345	4.449	**0.00**	
WHOQOL SRPB (total score)	-0.309	-3.670	**0.00**	

Table 3

Table 3. Logistic regression odds for remission of depressive symptoms* among depressed outpatients (n=111)

	Odds for remission			
Predictors	**OR**	**95% C.I.**	**Wald**	**Sig.**
Age	0.99	(0.93-1.05)	0.012	0.84
Female	0.35	(0.08-1.40)	2.180	0.05
Childhood abuse (CTQ)	0.99	(0.90-1.08)	0.039	0.66
Childhood neglect (CTQ)	1.01	(0.88-1.17)	0.052	0.75
Maudsley 1 (duration)	1.81	(0.54-6.07)	0.942	0.32
Maudsley 2 (severity)	0.59	(0.25-1.38)	1.468	0.21
Maudsley 3 (treatment failures)	0.60	(0.21-1.73)	0.870	0.38
Maudsley 4 (augmentation)	0.76	(0.16-3.65)	0.110	0.92
Social Support (MOS)	1.05	(1.00-1.09)	5.170	**0.02**
Religious Attendance (DUREL)	1.82	(1.08-3.07)	5.105	**0.02**
Private Practices (DUREL)	0.84	(0.50-1.42)	0.405	0.35
Intrinsic Religiosity (DUREL)	0.93	(0.68-1.27)	0.195	0.77
WHOQOL-SRPB	0.98	(0.72-1.34)	0.008	0.95

*Remission of depressive symptoms= HAM-D scores <7 within a 6 month follow-up (categorized into remission=1, no remission=0). Nagelkerke R Square 0.36, n=111, P=0.000. Significant variables in equation are underlined in bold for a P<0.05.

References

Amorim, P. (2000). Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev Bras Psiquiat., 22*, 106-115.

Bachmann, S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health, 15*(7). doi:10.3390/ijerph15071425

Bosworth, H. B., Park, K. S., McQuoid, D. R., Hays, J. C., & Steffens, D. C. (2003). The impact of religious practice and religious coping on geriatric depression. *Int J Geriatr Psychiatry, 18*(10), 905-914. doi:10.1002/gps.945

Braam, A. W., & Koenig, H. G. (2019). Religion, spirituality and depression in prospective studies: A systematic review. *J Affect Disord, 257*, 428-438. doi:10.1016/j.jad.2019.06.063

Braam, A. W., Schrier, A. C., Tuinebreijer, W. C., Beekman, A. T., Dekker, J. J., & de Wit, M. A. (2010). Religious coping and depression in multicultural Amsterdam: a comparison between native Dutch citizens and Turkish, Moroccan and Surinamese/Antillean migrants. *J Affect Disord, 125*(1-3), 269-278. doi:10.1016/j.jad.2010.02.116

Brietzke, E., Kauer Sant'anna, M., Jackowski, A., Grassi-Oliveira, R., Bucker, J., Zugman, A., . . . Bressan, R. A. (2012). Impact of childhood stress on psychopathology. *Braz J Psychiatry, 34*(4), 480-488. doi:10.1016/j.rbp.2012.04.009

Caldieraro, M. A., Baeza, F. L., Pinheiro, D. O., Ribeiro, M. R., Parker, G., & Fleck, M. P. (2013). Clinical differences between melancholic and nonmelancholic depression as defined by the CORE system. *Compr Psychiatry, 54*(1), 11-15. doi:10.1016/j.comppsych.2012.05.012

Caribe, A. C., Studart, P., Bezerra-Filho, S., Brietzke, E., Nunes Noto, M., Vianna-Sulzbach, M., . . . Miranda-Scippa, A. (2015). Is religiosity a protective factor against suicidal behavior in bipolar I outpatients? *J Affect Disord, 186*, 156-161. doi:10.1016/j.jad.2015.07.024

Dunner, D. L., Rush, A. J., Russell, J. M., Burke, M., Woodard, S., Wingard, P., & Allen, J. (2006). Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry, 67*(5), 688-695. doi:10.4088/jcp.v67n0501

Fazel, S., & Runeson, B. (2020). Suicide. *N Engl J Med, 382*(3), 266-274. doi:10.1056/NEJMra1902944

Fekadu, A., Donocik, J. G., & Cleare, A. J. (2018). Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry, 18*(1), 100. doi:10.1186/s12888-018-1679-x

Fleck, M. P., Berlim, M. T., Lafer, B., Sougey, E. B., Porto, J. A., Brasil, M. A., . . . Hetem, L. A. (2009). Review of the guidelines of the Brazilian Medical Association for the tratment of depression (Full version). *Rev Bras Psiquiat., 31*, 7-17.

Gaynes, B. N., Warden, D., Trivedi, M. H., Wisniewski, S. R., Fava, M., & Rush, J. A. (2009). What did STAR-D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatric Services, 60*(11). doi:https://doi.org/10.1176/ps.2009.60.11.1439

Grassi-Oliveira, R., Cogo-Moreira, H., Salum, G. A., Brietzke, E., Viola, T. W., Manfro, G. G., . . . Arteche, A. X. (2014). Childhood Trauma Questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. *PLoS One, 9*(1), e87118. doi:10.1371/journal.pone.0087118

Griep, R. H., Chor, D., Faerstein, E., Werneck, G. L., & Lopes, C. S. (2005). Construct validity of the Medical Outcomes Study's social support scale adapted to Portuguese in the Pró-Saúde Study. *Cad. Saúde Pública, 21*(3), 703-714. doi:doi: 10.1590/S0102-311X2005000300004

Gureje, O., Nortje, G., Makanjuola, V., Oladeji, B. D., Seedat, S., & Jenkins, R. (2015). The role of global traditional and complementary systems of medicine in the treatment of mental health disorders. *The Lancet Psychiatry, 2*(2), 168-177. doi:10.1016/s2215-0366(15)00013-9

Hackett, C., Grim, B. J., Cooperman, A., Ochoa, J. C., Gao, C., Shi, A. F., . . . Lugo, L. (2012). The Global Religious Landscape. A Report on the Size and Distribution of the World's Major Religious Groups as of 2010. *Pew Research Center*, 3-82. Retrieved from http://www.pewforum.org/global-religious-landscape.aspx

Hamilton, M. (1967). Development of a Rating Scale for Primary Depressive Illness. *Br J Soc Clin Psychol, 6*(4), 278-296. doi:DOI: 10.1111/j.2044-8260.1967.tb00530.x

Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2018). Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet*. doi:10.1016/s0140-6736(18)32408-5

Holvast, F., Burger, H., de Waal, M. M., van Marwijk, H. W., Comijs, H. C., & Verhaak, P. F. (2015). Loneliness is associated with poor prognosis in late-life depression: Longitudinal analysis of the Netherlands study of depression in older persons. *J Affect Disord, 185*, 1-7. doi:10.1016/j.jad.2015.06.036

Keller, M. B. (1992). Time to Recovery, Chronicity, and Levels of Psychopathology in Major Depression. *Archives of General Psychiatry, 49*(10). doi:10.1001/archpsyc.1992.01820100053010

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., . . . Group, C. D. W. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry, 61*(9), 540-560. doi:10.1177/0706743716659417

Koenig, H. G., George, L. K., & Peterson, B. L. (1998). Religiosity and Remission of Depression in Medically Ill Older Patients. *Am J Psychiatry, 155*(4), 536-542. doi:10.1176/ajp.155.4.536

Koenig, H. G., Peteet, J. R., & VanderWeele, T. J. (2020). Religion and psychiatry: clinical applications. *BJPsych Advances*, 1-9. doi:10.1192/bja.2020.11

Koenig, H. G., Zaben, F. A., & Khalifa, D. A. (2012). Religion, spirituality and mental health in the West and the Middle East. *Asian J Psychiatr, 5*(2), 180-182. doi:10.1016/j.ajp.2012.04.004

Krause, N., Hill, P. C., Emmons, R., Pargament, K. I., & Ironson, G. (2016). Assessing the Relationship Between Religious Involvement and Health Behaviors. *Health Education & Behavior, 44*(2), 278-284. doi:10.1177/1090198116655314

Lawrence, R. E., Oquendo, M. A., & Stanley, B. (2016). Religion and Suicide Risk: A Systematic Review. *Arch Suicide Res, 20*(1), 1-21. doi:10.1080/13811118.2015.1004494

Leskela, U., Rytsala, H., Komulainen, E., Melartin, T., Sokero, P., Lestela-Mielonen, P., & Isometsa, E. (2006). The influence of adversity and perceived social support on the outcome of major depressive disorder in subjects with different levels of depressive symptoms. *Psychol Med, 36*(6), 779-788. doi:10.1017/S0033291706007276

Li, S., Okereke, O. I., Chang, S.-C., Kawachi, I., & VanderWeele, T. J. (2016). Religious Service Attendance and Lower Depression Among Women—a Prospective Cohort Study. *Annals of Behavioral Medicine, 50*(6), 876-884. doi:10.1007/s12160-016-9813-9

Miller, L., Wickramaratne, P., Gameroff, M. J., Sage, M., Tenke, C. E., & Weissman, M. M. (2012). Religiosity and major depression in adults at high risk: a ten-year prospective study. *Am J Psychiatry, 169*(1), 89-94. doi:10.1176/appi.ajp.2011.10121823

Moreira-Almeida, A., Neto, F. L., & Koenig, H. G. (2006). Religiousness and mental health: a review. *Rev Bras Psiquiat., 28*, 242-250.

Moreira-Almeida, A., Pinsky, I., Zaleski, M., & Laranjeira, R. (2010). Religious involvement and sociodemographic factors: a Brazilian national survey. *Rev Psiq. Clín., 37*, 12-15.

Mosqueiro, B. P., da Rocha, N. S., & Fleck, M. P. d. A. (2015). Intrinsic religiosity, resilience, quality of life, and suicide risk in depressed inpatients. *J Affect Disord, 179*, 128-133. doi:10.1016/j.jad.2015.03.022

Pargament, K. I., & Lomax, J. W. (2013). Understanding and addressing religion among people with mental illness. *World Psychiatry, 12*(1), 26-32. doi:10.1002/wps.20005

Paterniti, S., Sterner, I., Caldwell, C., & Bisserbe, J. C. (2017). Childhood neglect predicts the course of major depression in a tertiary care sample: a follow-up study. *BMC Psychiatry, 17*(1), 113. doi:10.1186/s12888-017-1270-x

Richards, D. (2011). Prevalence and clinical course of depression: a review. *Clinical Psychology Review, 31*, 1117-1125. doi:10.1016/j.cpr.2011.07.004

Souza, L. H., Salum, G. A., Mosqueiro, B. P., Caldieraro, M. A., Guerra, T. A., & Fleck, M. P. (2016). Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. *J Affect Disord, 193*, 373-380. doi:10.1016/j.jad.2016.01.004

Taunay, T. C. D., Gondim, F. d. A. A., Macedo, D. S., Moreira-Almeida, A., Gurgel, L. d. A., Andrade, L. M. S., & Carvalho, A. F. (2012). Validity of the Brazilian version of the Duke Religion Index (DUREL). *Rev Psiq. Clín., 39*, 130-135.

Van den Brink, R. H. S., Schutter, N., Hanssen, D. J. C., Elzinga, B. M., Rabeling-Keus, I. M., Stek, M. L., . . . Oude Voshaar, R. C. (2018). Prognostic significance of social network, social support and loneliness for course of major depressive disorder in adulthood and old age. *Epidemiol Psychiatr Sci, 27*(3), 266-277. doi:10.1017/S2045796017000014

VanderWeele, T. J., Balboni, T. A., & Koh, H. K. (2017). Health and Spirituality. *JAMA, 318*(6), 519-520. doi:10.1001/jama.2017.8136

VanderWeele, T. J., Li, S., Tsai, A. C., & Kawachi, I. (2016). Association Between Religious Service Attendance and Lower Suicide Rates Among US Women. *JAMA Psychiatry, 73*(8), 845-851. doi:10.1001/jamapsychiatry.2016.1243

Vares, E. A., Salum, G. A., Spanemberg, L., Caldieraro, M. A., & Fleck, M. P. (2015). Depression Dimensions: Integrating Clinical Signs and Symptoms from the Perspectives of Clinicians and Patients. *PLoS One, 10*(8), e0136037. doi:10.1371/journal.pone.0136037

Verduijn, J., Verhoeven, J. E., Milaneschi, Y., Schoevers, R. A., van Hemert, A. M., Beekman, A. T. F., & Penninx, B. (2017). Reconsidering the prognosis of major depressive disorder across diagnostic boundaries: full recovery is the exception rather than the rule. *BMC Med, 15*(1), 215. doi:10.1186/s12916-017-0972-8

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., . . . Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and

International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord, 20*(2), 97-170. doi:10.1111/bdi.12609

Zimpel, R. R., Panzini, R. G., Bandeira, D. R., Fleck, M. P., & da Rocha, N. S. (2019). Psychometric properties of the WHOQOL-SRPB BREF, Brazilian Portuguese version. *Braz J Psychiatry, 41*(5), 411-418. doi:10.1590/1516-4446-2018-0083

10. ARTIGO #4

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Patient perspectives on spirituality and depression: Interest in spiritually integrated care among depressed patients in Brazil

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Introduction

Religion and spirituality represent a central domain for many individuals over different cultures worldwide (VanderWeele et al., 2017). In Brazil, 83.4% of population consider religion a very important aspect of their lives (Moreira-Almeida et al., 2010). Furthermore, evidence demonstrates that spirituality and religiosity (S/R) represent predominantly protective effects on mental health, especially for depressive disorders (Braam & Koenig, 2019). Yet, an integrated approach to depressed patients S/R in mental health care and psychotherapy remains a challenge (Rosmarin et al., 2020).

While spirituality and religiosity are both multifaceted constructs (King & Koenig, 2009), a commonly used definition in healthcare research distinguishes religion as an *organized and culture-bound system* of beliefs and practices designed to facilitate closeness to the sacred and transcendent, such as participation and involvement in religious rituals. Spirituality, on the other hand, is defined as a *personal* quest for the sacred and transcendent, regardless of whether it involves a religious group or community (Harold. G. Koenig et al., 2012). Thus, spirituality may involve understanding questions about life, meaning, and purpose outside of an organized framework that is shared with others.

Major depressive disorder (MDD) affects 300 million people worldwide and constitutes the leading cause of mental health-related disease burden in the world (Patel et al., 2016). Persistent and recurrent depressive symptoms cause significant suffering and prevent many people from fulfilling their potential, by impacting functionality and quality of life (Herrman et al., 2018). It is very common for individuals undergoing depressive episodes to turn to religion or spirituality as a coping strategy (K. I. Pargament & Lomax, 2013). Empirical studies suggest that S/R is mainly a protective factor to incident depression (Miller et al., 2012) and recovery of depressive episodes (Harold G. Koenig et al., 1998; Bruno Paz Mosqueiro et al., 2015). On the other hand, negative religious coping methods or religious struggles are consistently associated with more depression, and, therefore, should be properly identified in clinical practice (Rosmarin, Malloy, & Forester, 2014).

Considering the relationships between S/R and depression, it is of key importance for clinicians to conduct an open, interested and sensitive assessment of S/R, in order to understand the relationship of this domain to depressive symptoms (Peteet, 2012). Most patients prefer that S/R should have a role in their psychiatric care, and most individuals who receive spiritually sensitive care believe that it has a positive effect (Baetz, Griffin, Bowen, & Marcoux, 2004). Adding to that, religion and spirituality are connected to highly sensitive aspects of patient's lives, including culture, values, and identity. Therefore, spiritual life often represents key sources of meaning and purpose in the face of suffering (K. I. Pargament & Lomax, 2013). Spiritually integrated psychotherapies are therapeutic interventions that set into motion spiritual and religious content, along with conventional

psychotherapy approaches (Rosmarin et al., 2015). Randomized controlled studies suggest that these approaches demonstrate comparable benefits to standard interventions (N. Anderson et al., 2015) and might improve adherence to treatment for some patients (Lomax et al., 2011). Despite all of these trends, however, few studies have been conducted in Brazil to evaluate depressed patients' perceptions of S/R and interests in spiritually integrated care.

To these ends, the aims of this study were to evaluate the following in a sample of Brazilian depressed patients: (1) The perceived relevance of spirituality in their clinical care; (2) The extent to which patients were previously asked about S/R during treatment; (3) The willingness of patients to participate in spiritually integrated care; and (4) Clinical predictors of interest in spiritually integrated care.

Methods

Participants

We recruited individuals with a diagnosis of depression from an outpatient mood disorder program at the Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care university hospital in South Brazil. Patients were referred for specialized treatment of chronic, refractory, and severe depression by primary care settings and other outpatient medical clinics. All patients received a comprehensive psychiatric evaluation prior to treatment. From 234 individuals interviewed from May 2016 to November 2018, 166 presented with a diagnosis depression and completed the survey about their interest in religion, spirituality and spiritually integrated treatments for depressive disorders (figure 1). The sample included depressed patients with MDD (80.2%) but also BD patients facing depressive episodes (19.8%). All participants provided written informed consent, which was approved by the hospital ethical committee. Patients with severe clinical comorbidities or individuals with significant cognitive deficits that limited comprehension of self-report instruments and individuals with acute manic or hypomanic episodes were not included in the study.

Assessments

Psychiatric disorders were diagnosed by trained psychiatrists using the Brazilian-Portuguese version of Mini International Neuropsychiatric Interview (Amorim, 2000). All subjects underwent a comprehensive evaluation including a general protocol with clinical and socio-demographic information, and the Brazilian-Portuguese validated versions of Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967), Cumulative Illness Rating Scale (CIRS) (Salvi et al., 2008), Clinical Global Impression (CGI) (Lima et al., 2007), Childhood Trauma

Questionnaire (CTQ) (Grassi-Oliveira et al., 2014), Measurement of Parental Style (MOPS) (Baeza, Caldieraro, Pinheiro, & Fleck, 2010), Temperament & Personality Questionnaire (T&P) (Spanemberg et al., 2014), Resilience Scale (RS-14) (Wagnild, 2014), Medical Outcomes Study Social Support Index (MOS) (Griep et al., 2005) and World Health Organization Quality of Life Instrument (WHOQOL-Bref) (Fleck et al., 2000).

Religiosity

Religiosity was assessed using the Duke University Religion Index (DUREL), Brazilian-Portuguese validated version (Taunay et al., 2012). The instrument consists of 5 Likert-type questions, assessing three dimensions of religiosity. The first question evaluates the frequency of religious attendance (organizational religiosity), the second the frequency of private religious practices, such as prayer, meditation or reading religious (non-organizational religiosity) and the last three questions assess for intrinsic religiosity, which relates to the level of personal faith and commitment to a religious way of life.

Quality of Life/Spirituality

The brief version (8-items) of the Brazilian-Portuguese validated version of World Health Organization Quality of Life Spirituality, Religiousness and Personal Beliefs instrument (WHOQOL-SRPB) evaluated quality of life aspects related to spirituality (Panzini et al., 2011). WHOQOL-SRPB is a multidimensional instrument, developed in 18 different countries, that assesses for six domains of spiritual life: Connection (extent that connection to a spiritual being help through hard times); Meaning (extent that life has a purpose); Awe (extent that faith contributes to well-being); Wholeness (balance between mind, body and soul); Strength (extent that spiritual strength helps one to live better); Peace (extent of inner peace); Hope (extent of hope about life); and Faith (extent that faith give comfort in daily life). All 8-items in the measure sum to produce a single total score.

Interest in Spiritually Integrated Care

A general questionnaire was developed to evaluate whether patients wished to address S/R in their care, using the following four questions (yes/no): (1) Do you think it is important that health professionals question about S/R issues in health care consultations?; (2) Have you ever been questioned by any health care professional about S/R in a health care consultation?; (3) Do you think your S/R could eventually be against your treatment for depression (for instance, use of medications?); and (4) Would you participate in a psychotherapy including S/R issues in your treatment for depression?.

Statistical Analysis

All analyses were conducted with Statistical Package for Social Science (SPSS) version 20.0. First, descriptive information provided an overview of patient's perceptions regarding S/R in their treatment for depression. A descriptive perspective of interest in S/R care was compared across patients religious denominations and according the frequency of religious attendance in depressed patients.

Individuals interested in S/R care (*n* = 115) were then compared to those not interested (*n* = 52) across different demographic and clinical characteristics, using logistic regression models. The interest in spiritual integrated psychotherapy retrieved from question 4, providing categorical answers (interested=1, not interested=0) was the main dependent variable in our logistic regression models.

Clinical and socio-demographic variables were then tested as potential predictors of interest in spiritually integrated care, including socio-demographic variables, psychiatric comorbidities, bipolar disorder diagnostic, severity of depressive symptoms (HAM_D), childhood traumatic experiences (CTQ), perceived parental styles (MOPS), personality and temperament traits (T&P), resilience (RS-14), religiosity domains (DUREL) and WHOQOL-SRPB. Each variable studied in regression models was adjusted to the following socio-demographic variables (age, gender, ethnicity, education and employment). A $P < 0.05$ was considered statistically significant for all analysis.

Results

Sample Characteristics

The sample was comprised mainly by women (76.5 %), who were white (85.5%), and with a mean age of 51 years. Half the sample reported to be married (50.0%), and less than 20% of the patients were currently employed (16.3%). On average, patients reported more than three previous depressive episodes (3.35) with a mean of 18 years since diagnosis. Mean HAM-D scores (21.7; SD 4.91) are characteristic of patients with moderate to severe depressive symptoms in outpatient psychiatric care. Around 25% of patients reported a family history of suicide (24.0%), and almost half report a previous suicide attempt (43.1 %; Table 1).

Most patients presented with psychiatric comorbidities; 58.1 % of individuals presenting a depressive episode with melancholic features, 21.1% presented current psychosis, and 40.4% a lifetime history of psychosis. Comorbid Generalized Anxiety Disorder was diagnosed in 45.8% of individuals, followed by social anxiety in 20.5 % of patients.

The majority of patients reported affiliation with a religious group (82.8%), predominantly Catholicism (42.2%), Evangelical Christianity (20.6%) and Spiritism[2] (14.3%). For the non-religiously-affiliated (17.2%), 13.5% reported spiritual beliefs without a specific religious denomination (spiritual but not religious), and 2.2% defined themselves as Atheist (1.3%) or Agnostic (0.9%) (Table 2). Around 33% of patients reported attendance to a religious institution at least once a week, and another 30% a few times a month. One fifth (20%) of patients report private religious practices at least daily, such as prayer, meditation or religious readings.

Interest in S/R and Treatment for Depression

The vast majority of patients considered it important that professionals ask about spiritual or religious issues in health care consultations (82.1 %). However, only 36.9% reported ever being asked about S/R issues in their consultations. Almost all patients (96.4%) did not identify conflicts between their religious orientations treatment for depression, whereas 3% of patients (5 individuals) reported some kind of conflict (Figure 2).

Regarding preferences for spiritual care, 68.3% of patients reported that they would like to participate in spiritually integrated psychotherapy for the treatment of their depressive episode, whereas 31.1 % of patients did not wish to participate. Generally, individuals with more frequency of religious attendance reported *lower* interest in spiritually integrated care compared to individuals with lower attendance to religious groups or meetings (figure 3).

Predictors of Interest in Spiritually Integrated Psychotherapy

Different demographic and clinical variables were tested in logistic regression models as potential predictors of interest in spiritual integrated psychotherapy (question 4, interested=1, not-interested=0).

Demographic Predictors

The first logistic regression model included demographic variables (age, sex, ethnicity, education and employment) tested in logistic regression models as potential predictors of interest in spiritual integrated psychotherapy (interested=1, not-interested=0). Older age was a statistically significant predictor of greater interest in spiritually integrated care, albeit with a small effect size (OR 1.03, p = 0.02). Being employed was associated with

[2] Spiritism is a S/R doctrine originated in 19th century in France, embracing beliefs about survival of life after death, reincarnation, mediumship and Christian moral principles. It is widely practiced in Brazil and commonly searched as complementary spiritual care resource and social charity by Brazilian communities (Moreira-Almeida & Lotufo Neto, 2005).

marginally less interest in spiritual care (OR 0.94, *p* = 0.04). The other variables, otherwise, did not predict interest in spiritual care for depression including ethnicity, sex, and education levels.

Spiritual and Religious Predictors

Different S/R domains were tested as independent variables in logistic regression models as potential predictors of interest in spiritual integrated psychotherapy (interested=1, not-interested=0), controlling for demographics (age, gender, ethnicity, education and employment). Increased WHOQOL-SRPB scores (OR 1.15, p=0.04) were identified as a statistically significant predictor of interest in spiritual care. Other S/R dimensions, otherwise, did not predict interest in spiritual care, including religious denomination, religious attendance (DUREL), private practices (DUREL) and intrinsic religiosity (DUREL).

Clinical Predictors

Multiple clinical variables were tested as independent variables as potential predictors of interest in spiritually integrated psychotherapy (interested=1, not-interested=0) in logistic regression models, controlled for socio-demographics (age, gender, ethnicity, education and employment).

Severity of HAM-D depressive symptoms (OR 0.89, p=0.00), current psychosis (OR 0.38, p=0.02) and lifetime psychosis (OR 0.47, p=0.03) were statistically significantly associated with *less* interest in spiritually integrated care. Different clinical characteristics, otherwise, including bipolar disorder diagnostic (MINI), other psychiatric comorbidities (MINI), social support (MOS), resilience (RS-14), temperament and personality (T&P), childhood traumatic experiences (CTQ) and parental styles (MOPS) were not statistically significant predictors of interest in spiritual care (table 3).

Discussion

The present study identified religion and spirituality as important aspects in psychiatric care of Brazilian depressed outpatients. Most patients (82.1%) agreed that S/R should be routinely asked by their clinicians in consultations. Despite that, only 36.9% were previously asked in health care consultations about their S/R, even considering a long-term trajectory of illness (mean 13.8 years since the first diagnostic of depression, with mean 3 previous episodes).

The evidences supporting the inclusion of S/R in psychiatric evaluation include (1) the high prevalence and the relevance of S/R involvement in general population worldwide (Hackett et al., 2012); (2) the impact of S/R in mental health and outcomes of depressed patients (Braam & Koenig, 2019); (3) the perception that S/R beliefs, struggles or practices might influence psychiatric diagnosis and constitute relevant sources of information about the patient (K. I. Pargament & Lomax, 2013); (4) the fact that many patients would like that their clinicians take S/R in consideration along treatment (Moreira-Almeida et al., 2014); and (5) evidences suggesting that taking a spiritual history may have positive impacts on patients' outcome and satisfaction with treatments (VanderWeele et al., 2017).

Nevertheless, limited research has specifically investigated the interest of depressed patients in spiritual integrated treatments or their willingness to address those issues with their psychiatrists or therapists (Peteet, 2012). In different clinical settings S/R seem to play a significant role, especially for patients facing serious health conditions. A survey with palliative care patients in Canada, for instance, reported that 96.8% of patients identified as very or extremely important “receiving health care that is respectful and compassionate” and 55.4% “to have their spiritual or religious need met” in the context of end of life health treatment (Heyland et al., 2006). A systematic review of 54 studies (n=12,324) report that the majority of patients (70.5%) want to be asked by their doctors about S/R (Best, Butow, & Olver, 2015). The mentioned review included mainly patients facing life-threatening or chronic diseases (79.6%), most of them from United States (79.6%), and higher education, private insurance, personal religiosity, increased severity of patients illness and less intensity of S/R interaction were associated to an increased interest to discuss S/R in health care (Best et al., 2015).

Adding to that, despite a recognized difference in S/R beliefs and practices between psychiatrists and patients (*religious gap*), generally professionals agree about the relevance of addressing S/R issues in mental health care (Cook, 2011). A survey with 484 Brazilian psychiatrists, for instance, report that 76.8% of professionals considered very important to integrate patients S/R in clinical practice, but only 45.5% of them frequently inquire patients about that (Menegatti-Chequini et al., 2016). The most common barriers perceived included fear of exceeding ethical boundaries (30.2%), lack of training (22.3%) and lack of time (16.3%). Accordingly, German psychiatrists found appropriate to ask patients about S/R (75%), especially when patients bring these subject to discussion (90%). The most common reasons not to address S/R questions in clinical practice include concerns with professional neutrality (54.5%) and lack of time (34.3%) (Lee & Baumann, 2013). Considering the relevance of the matter, different mental health associations, including the American Psychiatric Association, American Psychological Association, Brazilian Psychiatric Association, Royal College of Psychiatrists and World Psychiatric Association (WPA) provide recommendations or sections to improve training and continuing education about S/R and mental health (Moreira-Almeida et al., 2014).

Our study also demonstrated that most depressed patients reported interest in spiritual care in their treatments (68.1%). The most significant predictors of interest in spiritually integrated care were severity of depressive symptoms and the presence of psychotic symptomatology, which were associated with less interest in spiritually integrated care. The fact that psychotic patients had less interest in spiritual integrated care flies in the face of stereotypes in psychiatry that psychosis is directly interested to religious or spiritual content (Rosmarin, Moreira-Almeida, & Koenig, 2018). The mentioned clinical characteristics possibly reflect a general decreased interest or motivation for any activity, including the interest in S/R questions, in patients experiencing severe acute depressive symptoms and psychotic symptoms (Braam & Koenig, 2019). On the contrary, increased WHOQOL-SRPB scores predicted greater willingness to participate in spiritually integrated treatment. WHOQOL-SRPB provide a measure of spiritual characteristics potentially addressed in spiritually integrated care, including positive mental health constructs as hope, meaning, faith, wholeness, potentially implicated with improvement of depressive symptoms (Panzini et al., 2011; Vaillant, 2013). Patients with more age and currently employed smaller predicting effects compared to the other mentioned variables.

Although not identified as a statically significant predictor in logistic regression models, patients with lower attendance to religious services showed trends suggesting higher interest in spiritually integrated care in descriptive analysis (figure 3). According to these finding, literature has demonstrated that patients with S/R beliefs but fewer S/R interaction might present increased interest to discuss their S/R questions in health care (Best et al., 2015). Among reasons to explain this finding it could be mentioned that patients with higher religious involvement might have already places to address and receive support in their S/R needs, a hypothesis reinforced by evidences in literature of protective effects of religious attendance to religious individuals (S. Li et al., 2016). Adding to that, people with clear religious beliefs may not feel comfortable having their S/R addressed by a mental health clinician since the latter tend to be irreligious (Menegatti-Chequini et al., 2016). On the contrary, patients with S/R beliefs but lower religious involvement in absence of a religious background would more opened to diverse spiritual experiences and willing to talk about their S/R with their psychiatrists or therapists (Willard & Norenzayan, 2017).

According to comprehensive review, spirituality is thought to influence treatments and could be integrated in psychotherapy in different ways (Captari et al., 2018): (1) as a source to improve understanding of the patient, exploring identity, cultural background, inner beliefs, S/R history, causes of distress, protective factors, and S/R struggles; (2) integrated with treatment goals, along with symptom reduction, as lifetime goals including increasing positive religious coping strategies, spiritual well being and relationship with sacred or divine; (3) S/R content integrated with traditional interventions such as behavioral activation, challenge negative thoughts, mindfulness; and (4) as a more broadened

psychotherapy perspective, spirituality as an integrative role of *self* addressing the relationships with sacred, and transcendent, as a framework to psychotherapy process (Captari et al., 2018; Peteet, 2012).

The effectiveness of spiritually integrated care has been studied recently, but still remain a key relevant research question (Harold G. Koenig, Peteet, et al., 2020). A metanalysis, for instance, identified 23 studies evaluating S/R interventions in mental health care. Generally, S/R interventions do not show statistically significant effects for depressive symptoms compared to control interventions. Two studies reported less depressive symptoms in post-traumatic stress disorder patients in one and six months of follow up (Gonçalves, Lucchetti, Menezes, & Vallada, 2015). Another recent metanalysis included 7 studies comparing faith adapted CBT with standard CBT interventions. Results demonstrated benefits of faith-adapted CBT for depression and identified that faith-adapted CBT could outperform standard CBT in some studies. Pooling all studies together, otherwise, the effect size for faith-adapted CBT was not statistically significant compared to standard CBT. After all, the high heterogeneity and limited number of studies in both metanalysis limited further conclusions (Anderson et al., 2015).

The presented results of our study should be considered considering a set of limitations. First, the cross-sectional evaluation does not allow causal inferences between variables. Furthermore, our study does not evaluate patient's interest in S/R or psychotherapy with a more comprehensive questions or controlling for the interest in psychotherapy without S/R content. Either, the results cannot be directly extrapolated to all groups of depressive individuals from Brazil, considering that the sample evaluated Brazilian depressive individuals in a tertiary care setting with more severe symptomatology. Despite that, results offer a consistent perspective of interest of Brazilian depressed patients in S/R and relevant findings to further research and clinical practice.

Conclusions

Religion and spirituality constitute a relevant aspect for most depressed patients, and should be routinely asked by their clinicians in clinical care.

References

Amorim, P. (2000). Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev Bras Psiquiat., 22*, 106-115.

Anderson, N., Heywood-Everett, S., Siddiqi, N., Wright, J., Meredith, J., & McMillan, D. (2015). Faith-adapted psychological therapies for depression and anxiety: Systematic review and meta-analysis. *J Affect Disord, 176*, 183-196. doi:10.1016/j.jad.2015.01.019

Baetz, M., Griffin, R., Bowen, R., & Marcoux, G. (2004). Spirituality and psychiatry in Canada: psychiatric practice compared with patient expectations. *Can J Psychiatry, 49*(4), 265-271. doi:10.1177/070674370404900407

Baeza, F. L. C., Caldieraro, M. A., Pinheiro, D. O., & Fleck, M. P. (2010). Translation and cross-cultural adaptation into Brazilian Portuguese of the Measure of Parental Style (MOPS) - a self-reported scale - according to the International Society for the Pharmacoeconomics and Outcomes Research (ISPOR) recommendations. *Rev Bras Psiquiat., 32*. doi:doi.org/10.1590/S1516-44462010000200011

Best, M., Butow, P., & Olver, I. (2015). Do patients want doctors to talk about spirituality? A systematic literature review. *Patient Educ Couns, 98*(11), 1320-1328. doi:10.1016/j.pec.2015.04.017

Braam, A. W., & Koenig, H. G. (2019). Religion, spirituality and depression in prospective studies: A systematic review. *J Affect Disord, 257*, 428-438. doi:10.1016/j.jad.2019.06.063

Captari, L. E., Hook, J. N., Hoyt, W., Davis, D. E., McElroy-Heltzel, S. E., & Worthington, E. L., Jr. (2018). Integrating clients' religion and spirituality within psychotherapy: A comprehensive meta-analysis. *J Clin Psychol, 74*(11), 1938-1951. doi:10.1002/jclp.22681

Cook, C. C. H. (2011). The faith of the psychiatrist. *Mental Health, Religion & Culture, 14*(1), 9-17. doi:10.1080/13674671003622673

Gonçalves, J. P. B., Lucchetti, G., Menezes, P. R., & Vallada, H. (2015). Religious and spiritual interventions in mental health care: a systematic review and meta-analysis of randomized controlled clinical trials. *Psychological Medicine, 45*(14), 2937-2949. doi:10.1017/s0033291715001166

Grassi-Oliveira, R., Cogo-Moreira, H., Salum, G. A., Brietzke, E., Viola, T. W., Manfro, G. G., . . . Arteche, A. X. (2014). Childhood Trauma Questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. *PLoS One, 9*(1), e87118. doi:10.1371/journal.pone.0087118

Griep, R. H., Chor, D., Faerstein, E., Werneck, G. L., & Lopes, C. S. (2005). Construct validity of the Medical Outcomes Study's social support scale adapted to Portuguese in the Pró-Saúde Study. *Cad. Saúde Pública, 21*(3), 703-714. doi:doi: 10.1590/S0102-311X2005000300004

Hackett, C., Grim, B. J., Cooperman, A., Ochoa, J. C., Gao, C., Shi, A. F., . . . Lugo, L. (2012). The Global Religious Landscape. A Report on the Size and Distribution of the World's Major Religious Groups as of 2010. *Pew Research Center*, 3-82. Retrieved from http://www.pewforum.org/global-religious-landscape.aspx

Hamilton, M. (1967). Development of a Rating Scale for Primary Depressive Illness. *Br J Soc Clin Psychol, 6*(4), 278-296. doi:DOI: 10.1111/j.2044-8260.1967.tb00530.x

Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2018). Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet*. doi:10.1016/s0140-6736(18)32408-5

Heyland, D. K., Dodek, P., Rocker, G., Groll, D., Gafni, A., Pichora, D., . . . Canadian Researchers End-of-Life, N. (2006). What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ, 174*(5), 627-633. doi:10.1503/cmaj.050626

King, M. B., & Koenig, H. G. (2009). Conceptualising spirituality for medical research and health service provision. *BMC Health Serv Res, 9*, 116. doi:10.1186/1472-6963-9-116

Koenig, H. G., Al-Zaben, F., & VanderWeele, T. J. (2020). Religion and psychiatry: recent developments in research. *BJPsych Advances*, 1-11. doi:10.1192/bja.2019.81

Koenig, H. G., George, L. K., & Peterson, B. L. (1998). Religiosity and Remission of Depression in Medically Ill Older Patients. *Am J Psychiatry, 155*(4), 536-542. doi:10.1176/ajp.155.4.536

Koenig, H. G., King, D. E., & Carson, V. B. (2012). *Handbook of Religion and Health*. New York, NY: Oxford University Press.

Koenig, H. G., Peteet, J. R., & VanderWeele, T. J. (2020). Religion and psychiatry: clinical applications. *BJPsych Advances*, 1-9. doi:10.1192/bja.2020.11

Lee, E., & Baumann, K. (2013). German psychiatrists' observation and interpretation of religiosity/spirituality. *Evid Based Complement Alternat Med, 2013*, 280168. doi:10.1155/2013/280168

Li, S., Okereke, O. I., Chang, S.-C., Kawachi, I., & VanderWeele, T. J. (2016). Religious Service Attendance and Lower Depression Among Women—a Prospective Cohort Study. *Annals of Behavioral Medicine, 50*(6), 876-884. doi:10.1007/s12160-016-9813-9

Lima, M. S., Soares, B. G., Paoliello, G., Machado Vieira, R., Martins, C. M., Mota Neto, J. I., . . . Volpe, F. M. (2007). The Portuguese version of the Clinical Global Impression-Schizophrenia Scale: validation study. *Braz J Psychiatry, 29*(3), 246-249. doi:10.1590/s1516-44462007000300010

Lomax, J. W., Kripal, J. J., & Pargament, K. I. (2011). Perspectives on "Sacred Moments" in Psychotherapy. *Am J Psychiatry, 168*.

Menegatti-Chequini, M. C., Goncalves, J. P., Leao, F. C., Peres, M. F., & Vallada, H. (2016). A preliminary survey on the religious profile of Brazilian psychiatrists and their approach to patients' religiosity in clinical practice. *BJPsych Open, 2*(6), 346-352. doi:10.1192/bjpo.bp.116.002816

Miller, L., Wickramaratne, P., Gameroff, M. J., Sage, M., Tenke, C. E., & Weissman, M. M. (2012). Religiosity and major depression in adults at high risk: a ten-year prospective study. *Am J Psychiatry, 169*(1), 89-94. doi:10.1176/appi.ajp.2011.10121823

Moreira-Almeida, A., Koenig, H. G., & Lucchetti, G. (2014). Clinical implications of spirituality to mental health: review of evidence and practical guidelines. *Revista Brasileira de Psiquiatria, 36*(2), 176-182. doi:10.1590/1516-4446-2013-1255

Moreira-Almeida, A., Pinsky, I., Zaleski, M., & Laranjeira, R. (2010). Religious involvement and sociodemographic factors: a Brazilian national survey. *Rev Psiq. Clín., 37*, 12-15.

Mosqueiro, B. P., da Rocha, N. S., & Fleck, M. P. d. A. (2015). Intrinsic religiosity, resilience, quality of life, and suicide risk in depressed inpatients. *J Affect Disord, 179*, 128-133. doi:10.1016/j.jad.2015.03.022

Panzini, R. G., Maganha, C., Rocha, N. S., Bandeira, D. R., & Fleck, M. P. (2011). Brazilian validation of the Quality of Life Instrument/spirituality, religion and personal beliefs. *Rev Saude Publica, 45*(1), 153-165.

Pargament, K. I., & Lomax, J. W. (2013). Understanding and addressing religion among people with mental illness. *World Psychiatry, 12*(1), 26-32. doi:10.1002/wps.20005

Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., . . . Whiteford, H. (2016). Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *The Lancet, 387*(10028), 1672-1685. doi:10.1016/s0140-6736(15)00390-6

Peteet, J. R. (2012). Spiritually integrated treatment of depression: a conceptual framework. *Depress Res Treat, 2012*, 124370. doi:10.1155/2012/124370

Rosmarin, D. H., Forester, B. P., Shassian, D. M., Webb, C. A., & Bjorgvinsson, T. (2015). Interest in spiritually integrated psychotherapy among acute psychiatric patients. *J Consult Clin Psychol, 83*(6), 1149-1153. doi:10.1037/ccp0000046

Rosmarin, D. H., Malloy, M. C., & Forester, B. P. (2014). Spiritual struggle and affective symptoms among geriatric mood disordered patients. *Int J Geriatr Psychiatry, 29*(6), 653-660. doi:10.1002/gps.4052

Rosmarin, D. H., Moreira-Almeida, A., & Koenig, H. (2018). Religion and psychotic experiences. *Acta Psychiatr Scand, 138*(2), 173. doi:10.1111/acps.12917

Rosmarin, D. H., Pargament, K. I., & Koenig, H. G. (2020). Spirituality and mental health: challenges and opportunities. *Lancet Psychiatry*. doi:10.1016/S2215-0366(20)30048-1

Salvi, F., Miller, M. D., Grilli, A., Giorgi, R., Towers, A. L., Morichi, V., . . . Dessi-Fulgheri, P. (2008). A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc, 56*(10), 1926-1931. doi:10.1111/j.1532-5415.2008.01935.x

Spanemberg, L., Salum, G. A., Caldieraro, M. A., Vares, E. A., Tiecher, R. D., da Rocha, N. S., . . . Fleck, M. P. (2014). Personality styles in depression: Testing reliability and validity of hierarchically organized constructs. *Personality and Individual Differences, 70*, 72-79. doi:10.1016/j.paid.2014.06.021

Taunay, T. C. D., Gondim, F. d. A. A., Macedo, D. S., Moreira-Almeida, A., Gurgel, L. d. A., Andrade, L. M. S., & Carvalho, A. F. (2012). Validity of the Brazilian version of the Duke Religion Index (DUREL). *Rev Psiq. Clín., 39*, 130-135.

Vaillant, G. E. (2013). Psychiatry, religion, positive emotions and spirituality. *Asian J Psychiatr, 6*(6), 590-594. doi:10.1016/j.ajp.2013.08.073

VanderWeele, T. J., Balboni, T. A., & Koh, H. K. (2017). Health and Spirituality. *JAMA, 318*(6), 519-520. doi:10.1001/jama.2017.8136

Wagnild, G. M. (2014). *The Resilience Scale User's Guide* (P. E. Guinn Ed.). Montana, United States of America: Resilience Center.

Willard, A. K., & Norenzayan, A. (2017). "Spiritual but not religious": Cognition, schizotypy, and conversion in alternative beliefs. *Cognition, 165*, 137-146. doi:10.1016/j.cognition.2017.05.018

Zimpel, R. R., Panzini, R. G., Bandeira, D. R., Fleck, M. P., & da Rocha, N. S. (2019). Psychometric properties of the WHOQOL-SRPB BREF, Brazilian Portuguese version. *Braz J Psychiatry, 41*(5), 411-418. doi:10.1590/1516-4446-2018-0083

Figure 1. Flowchart of patient's inclusion

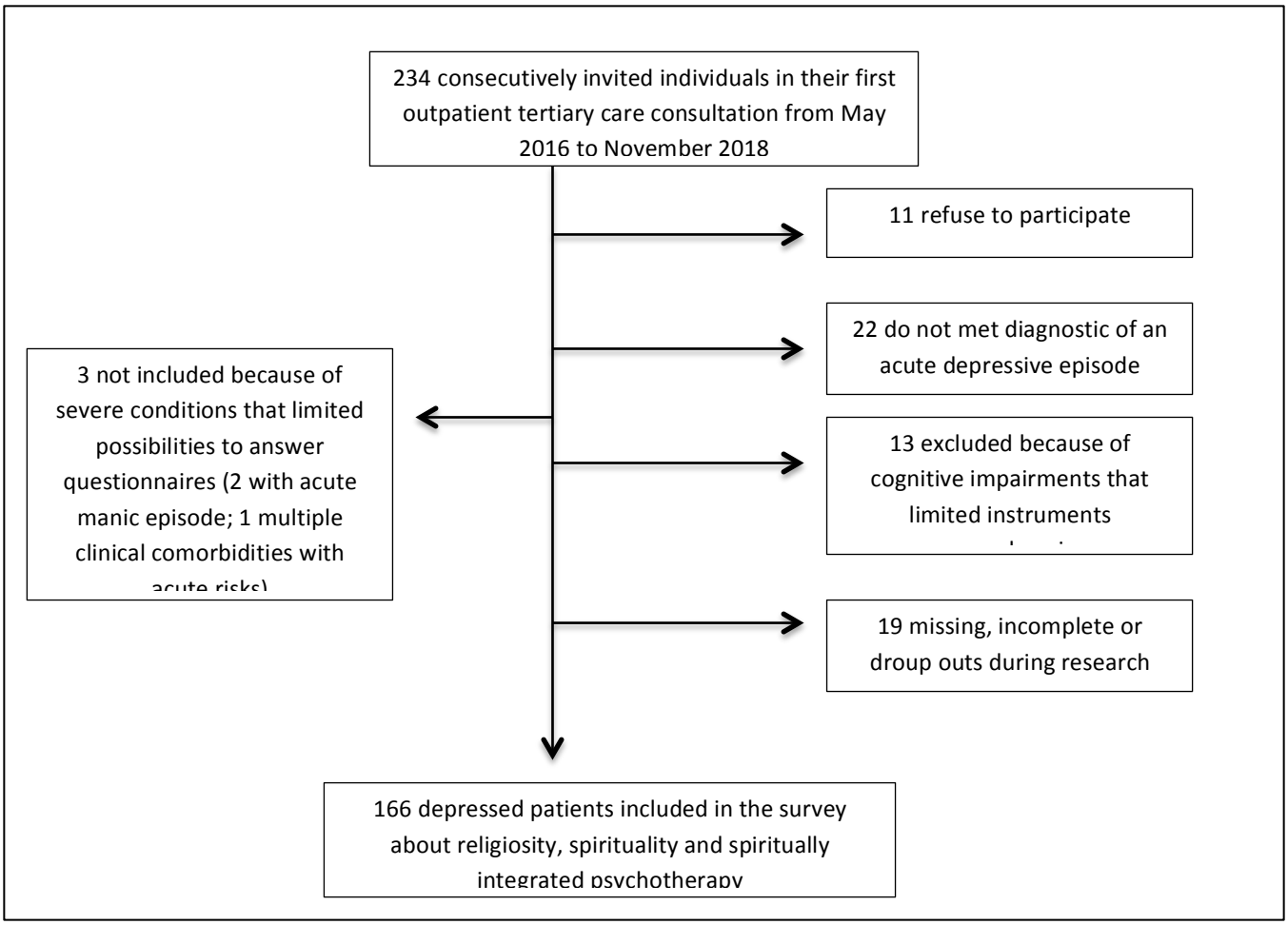


Table 1.

Table 1. Socio-Demographic and Clinical Variables of Depressed Patients (n=166)

	Freq.	Perc. (%)
Female	127	76.5
Male	39	23.5
White	142	85.5
Non-White	24	14.5
Single	20	12.0
Married	83	50.0
Divorced	42	25.3
Widowed	21	12.7
Employed	27	16.3
Unemployed	40	24.1
Stay at home	17	10.2
Student	3	1.8
Retired	10	6.0
Health insurance	57	34.4
Familiar History of Suicide	40	24.0
Previous Suicide Attempt	72	43.1
Psychiatric Comorbidities		
Melancholic Features	97	58.1
Current Psychosis	35	21.1
Previous Psychosis	67	40.4
Panic Disorder	28	16.9
Social Phobia	34	20.5
OCD	25	15.1
PTSD	12	7.2
GAD	76	45.8

	Range	Mean	(SD)
Age	18-75	51.2	11.3
Education (years study)	0-22	8.61	3.88
Age of Onset Depression	6-68	33.0	14.8
Number of Depressive Episodes	1-10	3.35	2.56
Years Since the First Episode	1-57	18.3	13.3
Clinical Global Impression (CGI)	0-7	4.85	0.89
Social Support (MOS)	22-95	64.6	18.2
Resilience (RS-14)	16-84	55.8	14.8
Depressive symptoms (HAM-D)	8-35	21.7	4.91

Table 2.

Table 2. Interest in spirituality integrated care and religious affiliation among depressed outpatients in Brazil (n=166)

Religious Affiliation	**Freq.**	**Perc. (%)**	**Not Interested (%/n)**	**Interested (%/n)**
Affiliated	133	82.8	30.1 (40)	69.9 (93)
Non-Affiliated	34	17.2	35.3 (12)	64.7 (22)
Catholic	94	42.2	27.1 (19)	72.9 (51)
Evangelical Religions	46	20.6	34.6 (9)	65.4 (17)
Spiritism	32	14.3	25.9 (7)	74.1 (20)
Afro-Brazilian Religions	7	3.1	25.0 (1)	75.0 (3)
Spiritual But Not Religious	29	13.5	27.6 (8)	72.4 (21)
Agnosticism	2	0.9	100 (2)	0 (0)
Atheism	3	1.3	66.7 (2)	33.3 (1)

Figure 2.

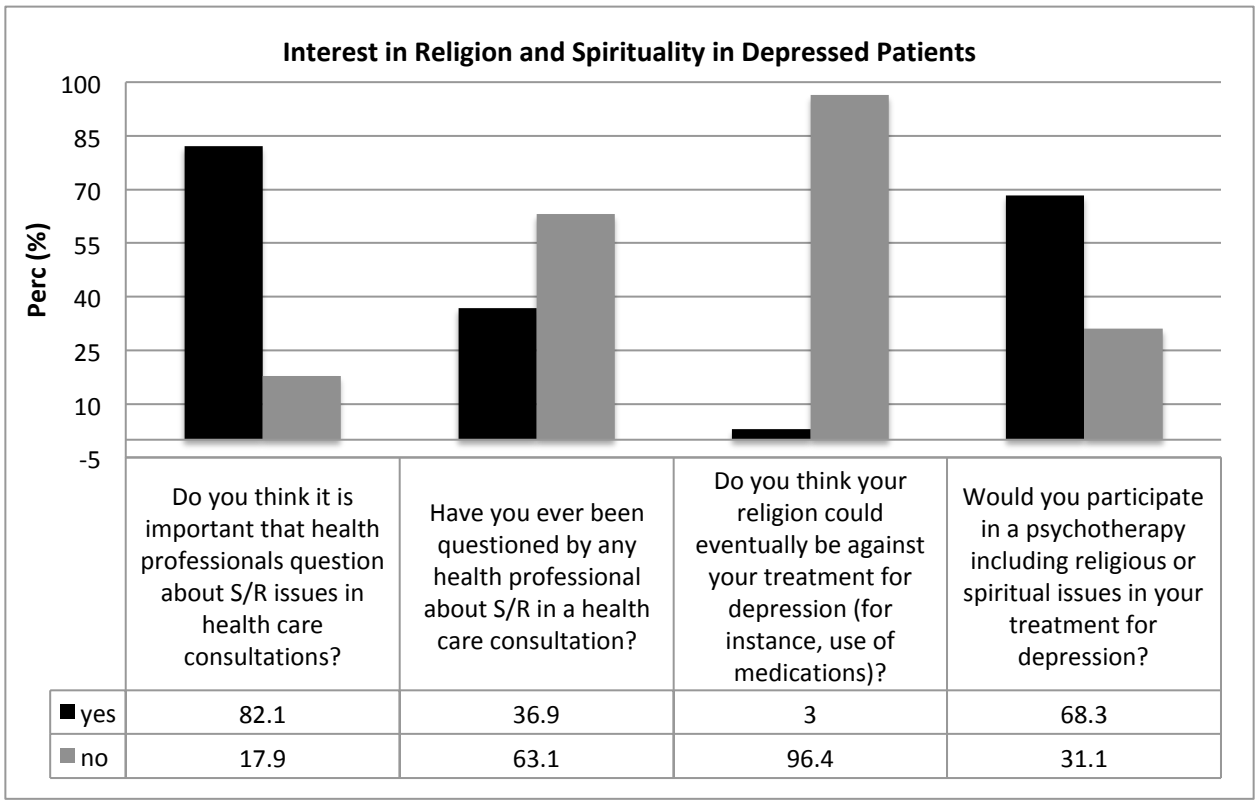
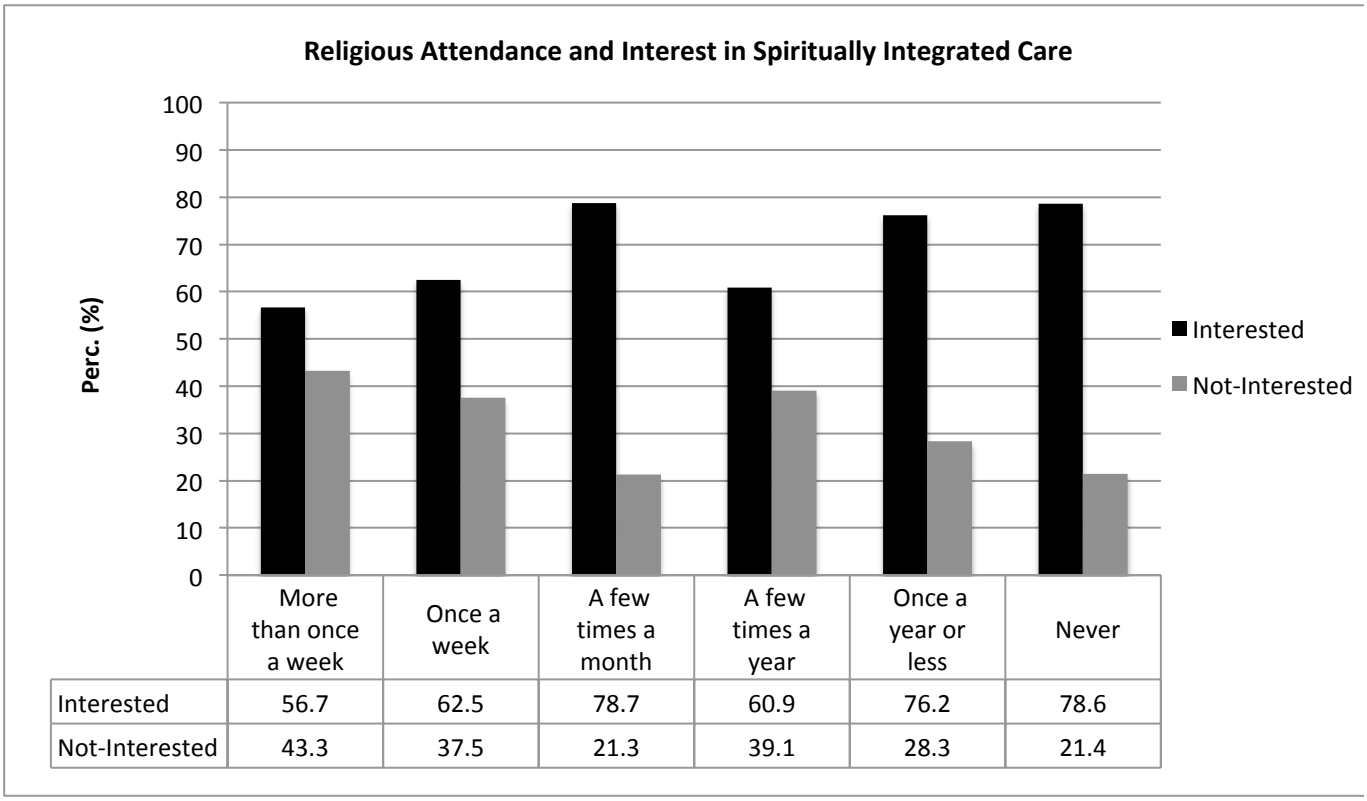


Figure 2. Perceptions about spirituality and religion (S/R) integration in the treatment of depressed outpatients in Brazil (n=166).

Figure 3.



	More than once a week	Once a week	A few times a month	A few times a year	Once a year or less	Never
Interested	56.7	62.5	78.7	60.9	76.2	78.6
Not-Interested	43.3	37.5	21.3	39.1	28.3	21.4

Figure 3. Religious attendance (DUREL Organizational Religiosity) and interest in spiritually integrated care (n=166).

Table 3. Predictors of Interest in Spiritual Integrated Psychotherapy in Depressed Patients Logistic Regression Model (n=166)

	Interest in Spiritually Integrated Care			
	Odds Ratio	**95% C.I.**	**Wald**	**P-value**
Logistic Regression Demographics				
Age*	1.03	(1.01-1.07)	5.197	**0.02**
Gender	0.93	(0.40-2.13)	0.028	0.86
Ethnicity	2.48	(0.83-7.36)	2.696	0.10
Education	0.94	(0.86-1.02)	1.856	0.17
Employed*	0.94	(0.15-0.95)	4.208	**0.04**
Multivariate Logistic Regression Models**				
Religiosity	**Odds Ratio**	**95% C.I.**	**Wald**	**P-value**
Catholic	1.21	(0.57-2.56)	0.249	0.61
Evangelical	0.72	(0.28-1.83)	0.458	0.49
Spiritism	1.64	(0.59-4.57)	0.920	0.33
Afro-Brazilian Religions	1.22	(0.11-13.34)	0.027	0.87
Spiritual But Not Religious	1.45	(0.54-3.92)	0.559	0.45
Agnostic/Atheist	0.32	(0.02-4.09)	0.747	0.38
Religious Attendance (DUREL)	1.09	(0.85-1.39)	0.520	0.47
Private Practices (DUREL)	1.18	(0.96-1.45)	2.584	0.10
Intrinsic Religiosity (DUREL)	1.08	(0.97-1.21)	2.436	0.11
Spiritual Quality of Life (WHOQOL-SRPB)*	1.15	(1.01-1.32)	4.197	**0.04**
Clinical Variables				
Depressive Symptoms (HAM-D)*	0.89	(0.83-0.96)	7.849	**0.00**
Melancholic Features (MINI)	0.64	(0.31-1.33)	1.405	0.23
Current Psychosis (MINI)*	0.38	(0.16-0.88)	5.052	**0.02**
Lifetime Psychosis (MINI)*	0.47	(0.23-0.96)	4.264	**0.03**
Previous Hypomania (MINI)	0.53	(0.16-1.72)	1.091	0.29
Previous Mania (MINI)	4.24	(0.90-19.94)	3.360	0.06
Panic Disorder (MINI)	0.69	(0.27-1.76)	0.575	0.44
Social Phobia (MINI)	1.76	(0.70-4.46)	1.455	0.22
OCD (MINI)	1.76	(0.63-4.93)	1.173	0.27
PTSD (MINI)	6.47	(0.76-54.64)	2.946	0.08
GAD (MINI)	0.94	(0.46-1.90)	0.028	0.86
Cumulative Illness Rating Scale (CIRS)	0.96	(0.86-1.07)	0.406	0.52
Social Support (MOS)	1.00	(0.98-1.02)	0.047	0.82
Resilience (RS-14)	1.01	(0.99-1.04)	2.093	0.14
Temperament & Personality (T&P)				
Anxious	0.99	(0.92-1.06)	0.016	0.90
Reserve	1.00	(0.94-1.06)	0.000	0.99
Irritability	1.00	(0.95-1.06)	0.049	0.82
Perfectionism	0.99	(0.93-1.05)	0.076	0.78
Childhood Traumatic Experiences (CTQ)				
Emotional Abuse	0.98	(0.92-1.04)	0.215	0.64
Physical Abuse	1.01	(0.92-1.10)	0.076	0.78
Sexual Abuse	0.99	(0.90-1.09)	0.016	0.90
Emotional Neglect	1.01	(0.93-1.10)	0.164	0.68
Physical Neglect	0.99	(0.90-1.09)	0.006	0.93
Measure of Parental Style (MOPS)				
Indifference Mother	1.01	(0.94-1.08)	0.117	0.73
Abuse Mother	1.02	(0.94-1.11)	0.403	0.52
Overcontrol Mother	0.97	(0.86-1.09)	0.174	0.67

Indifference Father	0.99	(0.92-1.05)	0.079	0.77
Abuse Father	1.05	(0.96-1.14)	1.296	0.25
Overcontrol Father	1.10	(0.96-1.27)	2.129	0.14

*Statistically significant results in bold ($p<0.05$). **Variables individually adjusted for Age, Gender, Ethnicity, Education and Employment.

10. CONSIDERACOES FINAIS

Perspectivas históricas relacionando religiosidade à psicopatologia, desde autores no início do século XX como Sigmund Freud ou Albert Ellis, perpassando menções a R/E de forma predominante ligada a sintomas ou transtornos mentais em publicações e textos psiquiátricos de referência, contribuíram para distanciamento dos profissionais da saúde do estudo e entendimento do papel da religiosidade e espiritualidade na saúde mental (Koenig et al., 2020). Entretanto, evidências científicas das últimas décadas confirmam uma relação predominantemente positiva da R/E para saúde mental, bem-estar e qualidade de vida das pessoas (Cloninger, 2006). Além disso, muitos estudos corroboram o interesse de muitos pacientes em abordar essa temática em seus atendimentos de saúde (Rosmarin et al., 2015). Efeitos relevantes e consistentes da R/E são observados na prevenção e tratamento da depressão e ainda mais significativos para prevenção do suicídio e uso de substâncias (Koenig et al., 2020).

Nesse sentido a presente tese de Doutorado contribui para pesquisa e prática clínica na psiquiatria a partir da investigação dos efeitos da religiosidade e espiritualidade sobre diversas perspectivas em pacientes graves com depressão. Como contribuição relevante, traz evidências sobre o impacto da R/E na depressão a partir da consideração cultural e de crenças de pacientes brasileiros. Os estudos apresentados identificam a importância do tema percebido pelos pacientes, apresentam possíveis mediadores de efeito da R/E na depressão e ressaltam os efeitos significativos da R/E em desfechos clínicos relevantes no tratamento da depressão.

Como achados significativos destacamos no Artigo#1 a identificação de correlações significativas entre religiosidade intrínseca e níveis maiores de BDNF séricos em pacientes com depressão internados em Unidade Psiquiátrica. Trata-se de estudo original, que contribui para pesquisa internacional e entendimento de mediadores biológicos dos efeitos da religiosidade e espiritualidade na depressão. Os achados do estudo identificam efeito significativo da religiosidade intrínseca sobre BDNF, marcador biológico associado a recuperação de sintomas depressivos e possível marcador neuroplasticidade cerebral. Os achados estão de acordo com literatura científica recente que relaciona maior religiosidade a efeitos protetores para depressão, incluindo dados de estudos prospectivos consistentes relacionando a R/E a menor incidência de depressão e maior recuperação de sintomas depressivos, além de achados de maior espessura cortical em indivíduos que relatam que a R/E possui maior importância em suas vidas.

No Artigo#2 exploramos possíveis relações entre domínios da R/E, fatores positivos e sintomas depressivos, utilizando metodologia de análise estatística de redes *(network analysis)*. Trata-se de estudo original, utilizando metodologia de análise estatística não

direcionada (*data-driven)* com crescente uso em estudos sobre depressão. As análises de rede permitem a visualização das relações entre os diversos domínios da R/E e depressão, e permitem um entendimento de quais características possuem maior relevância ou centralidade na rede. Além disso, contribuem para identificação de possíveis mecanismos de ação da R/E a partir do entendimento das relações entre as variáveis estudadas. Entre os achados relevantes do estudo, identificamos o papel dos fatores positivos (e.g. resiliência, esperança, força espiritual, bem-estar espiritual e propósito) como potenciais caminhos ou mediadores de efeito da religiosidade nos sintomas depressivos. Os diversos domínios da religiosidade avaliados através da Escala de Religiosidade de Duke (organizacional, não-organizacional e intrínseca) apresentam relações independentes com fatores positivos avaliados através do instrumento de qualidade de vida relacionada a religiosidade, espiritualidade e crenças pessoais da OMS (WHOQOL-SRPB). De forma interessante, e de acordo com estudos descritos na literatura, a percepção de suporte social não se mostrou como mediador central dos efeitos positivos da religiosidade na depressão, apresentando efeitos independentes com o instrumento WHOQOL-SRPB.

No Artigo#3 identificamos o efeito clínico relevante da religiosidade organizacional (especificamente frequência a encontros religiosos) como principal preditor de remissão de sintomas depressivos em seguimento prospectivo de 6 meses de pacientes com depressão. Conforme achados do estudo, pacientes com maior frequência a encontros religiosos apresentaram 83% maiores chances de remissão dos sintomas ao longo dos 6 meses de seguimento comparados aos pacientes com menor frequência a encontros religiosos. Além disso, dimensões da R/E como religiosidade intrínseca, religiosidade organizacional, e escores do WHOQOL-SRPB foram relacionados de forma significativa e inversa aos escores de risco de suicídio dos pacientes com depressão. Ressalta-se a relevância dos resultados em uma amostra de pacientes graves, com múltiplas comorbidades clínicas e vulnerabilidades psicossociais e a importância de abordar a temática na prática clínica psiquiátrica. Tais achados reforçam a importância clínica da R/E como fator potencialmente associado a desfechos relevantes, incluindo risco de suicídio e melhora de sintomas depressivos ao longo do tratamento.

No Artigo#4, por fim, identificamos a importância do tema para os pacientes, incluindo o interesse na integração da R/E no seu tratamento e participação em psicoterapias integradas a espiritualidade. De forma surpreendente, a maior parte dos pacientes refere nunca ter sido questionado por profissionais da saúde sobre sua religiosidade ou espiritualidade. Além disso, a maior parte dos pacientes relata interesse em participar de uma psicoterapia integrada a espiritualidade, modalidade de tratamento que inclui aspectos ligados a R/E dos pacientes nos modelos de psicoterapia convencionais. O estudo demonstra o hiato existente entre a importância que os pacientes dão para o tema, e o pouco investimento dos profissionais de saúde para avaliá-lo. Tais resultados reforçam a

importância de iniciativas que promovam educação e treinamentos para melhorar a avaliação e compreensão do tema na psiquiatria e saúde mental.

Como perspectivas futuras destacamos a relevância da pesquisa científica e olhar investigativo para aprofundar o entendimento sobre os mecanismos através dos quais a R/E exerce seus efeitos na saúde mental, incluindo fatores biológicos e psicossociais, em diferentes culturas e cenários clínicos. Adicionalmente, identificamos a relevância de estudos com estratégias de integração da espiritualidade na avaliação e prática clínica de forma ética, aberta, e baseada em evidências. Intervenções integradas a espiritualidade constituem recursos relevantes para aprimorar estratégias de tratamento baseadas nos interesses dos pacientes, incluindo fatores que podem melhorar desfechos da depressão e prevenção ao suicídio. Além disso, se torna de grande a importância o ensino e educação continuada sobre religiosidade e espiritualidade de modo a ampliar as possibilidades dos profissionais de saúde para abordar a temática da melhor forma na prática clínica.

Ressaltamos, enfim, a importante contribuição da ciência e da pesquisa na investigação e do entendimento de temas ligados a religiosidade e espiritualidade, e a importante contribuição e dedicação dos pacientes participantes dos estudos, permitindo novos olhares e perspectivas sobre esse tema, de grande relevância para população brasileira e mundial e em especial para muitos outros pacientes em tratamento da depressão.

11. REFERENCIAS

Aizawa, S., Ishitobi, Y., Masuda, K., Inoue, A., Oshita, H., Hirakawa, H., . . . Akiyoshi, J. (2015). Genetic association of the transcription of neuroplasticity-related genes and variation in stress-coping style. *Brain and Behavior, 5*(9), n/a-n/a. doi:10.1002/brb3.360

Alimujiang, A., Wiensch, A., Boss, J., Fleischer, N. L., Mondul, A. M., McLean, K., . . . Pearce, C. L. (2019). Association Between Life Purpose and Mortality Among US Adults Older Than 50 Years. *JAMA Netw Open, 2*(5), e194270. doi:10.1001/jamanetworkopen.2019.4270

Amorim, P. (2000). Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. *Rev Bras Psiquiat., 22*, 106-115.

Anderson, J. W., & Nunnelley, P. A. (2016). Private prayer associations with depression, anxiety and other health conditions: an analytical review of clinical studies. *Postgrad Med, 128*(7), 635-641. doi:10.1080/00325481.2016.1209962

Anderson, N., Heywood-Everett, S., Siddiqi, N., Wright, J., Meredith, J., & McMillan, D. (2015). Faith-adapted psychological therapies for depression and anxiety: Systematic review and meta-analysis. *J Affect Disord, 176*, 183-196. doi:10.1016/j.jad.2015.01.019

Anyfantakis, D., Symvoulakis, E. K., Linardakis, M., Shea, S., Panagiotakos, D., & Lionis, C. (2015). Effect of religiosity/spirituality and sense of coherence on depression within a rural population in Greece: the Spili III project. *BMC Psychiatry, 15*, 173. doi:10.1186/s12888-015-0561-3

Bachmann, S. (2018). Epidemiology of Suicide and the Psychiatric Perspective. *Int J Environ Res Public Health, 15*(7). doi:10.3390/ijerph15071425

Baetz, M., Griffin, R., Bowen, R., & Marcoux, G. (2004). Spirituality and psychiatry in Canada: psychiatric practice compared with patient expectations. *Can J Psychiatry, 49*(4), 265-271. doi:10.1177/070674370404900407

Baeza, F. L. C., Caldieraro, M. A., Pinheiro, D. O., & Fleck, M. P. (2010). Translation and cross-cultural adaptation into Brazilian Portuguese of the Measure of Parental Style (MOPS) - a self-reported scale - according to the International Society for the Pharmacoeconomics and Outcomes Research (ISPOR) recommendations. *Rev Bras Psiquiat., 32*. doi:doi.org/10.1590/S1516-44462010000200011

Beam, A. L., & Kohane, I. S. (2018). Big Data and Machine Learning in Health Care. *JAMA, 319*(13), 1317-1318. doi:10.1001/jama.2017.18391

Beard, C., Millner, A. J., Forgeard, M. J., Fried, E. I., Hsu, K. J., Treadway, M. T., . . . Bjorgvinsson, T. (2016). Network analysis of depression and anxiety symptom relationships in a psychiatric sample. *Psychol Med, 46*(16), 3359-3369. doi:10.1017/S0033291716002300

Beauregard, M., & Paquette, V. (2006). Neural correlates of a mystical experience in Carmelite nuns. *Neurosci Lett, 405*(3), 186-190. doi:10.1016/j.neulet.2006.06.060

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. *Mol Psychiatry, 24*(6), 888-900. doi:10.1038/s41380-019-0385-5

Best, M., Butow, P., & Olver, I. (2015). Do patients want doctors to talk about spirituality? A systematic literature review. *Patient Educ Couns, 98*(11), 1320-1328. doi:10.1016/j.pec.2015.04.017

Bonelli, R., Dew, R. E., Koenig, H. G., Rosmarin, D. H., & Vasegh, S. (2012). Religious and Spiritual Factors in Depression: Review and Integration of the Research. *Depression Research and Treatment, 2012*, 1-8. doi:10.1155/2012/962860

Bonelli, R. M., & Koenig, H. G. (2013). Mental disorders, religion and spirituality 1990 to 2010: a systematic evidence-based review. *J Relig Health, 52*(2), 657-673. doi:10.1007/s10943-013-9691-4

Borrelli, E., Nestler, E. J., Allis, C. D., & Sassone-Corsi, P. (2008). Decoding the Epigenetic Language of Neuronal Plasticity. *Neuron, 60*(6), 961-974. doi:10.1016/j.neuron.2008.10.012

Bosworth, H. B., Park, K. S., McQuoid, D. R., Hays, J. C., & Steffens, D. C. (2003). The impact of religious practice and religious coping on geriatric depression. *Int J Geriatr Psychiatry, 18*(10), 905-914. doi:10.1002/gps.945

Braam, A. W., & Koenig, H. G. (2019). Religion, spirituality and depression in prospective studies: A systematic review. *J Affect Disord, 257*, 428-438. doi:10.1016/j.jad.2019.06.063

Braam, A. W., Schrier, A. C., Tuinebreijer, W. C., Beekman, A. T., Dekker, J. J., & de Wit, M. A. (2010). Religious coping and depression in multicultural Amsterdam: a comparison between native Dutch citizens and Turkish, Moroccan and Surinamese/Antillean migrants. *J Affect Disord, 125*(1-3), 269-278. doi:10.1016/j.jad.2010.02.116

Brietzke, E., Kauer Sant'anna, M., Jackowski, A., Grassi-Oliveira, R., Bucker, J., Zugman, A., . . . Bressan, R. A. (2012). Impact of childhood stress on psychopathology. *Braz J Psychiatry, 34*(4), 480-488. doi:10.1016/j.rbp.2012.04.009

Caldieraro, M. A., Baeza, F. L., Pinheiro, D. O., Ribeiro, M. R., Parker, G., & Fleck, M. P. (2013). Clinical differences between melancholic and nonmelancholic depression as defined by the CORE system. *Compr Psychiatry, 54*(1), 11-15. doi:10.1016/j.comppsych.2012.05.012

Captari, L. E., Hook, J. N., Hoyt, W., Davis, D. E., McElroy-Heltzel, S. E., & Worthington, E. L., Jr. (2018). Integrating clients' religion and spirituality within psychotherapy: A comprehensive meta-analysis. *J Clin Psychol, 74*(11), 1938-1951. doi:10.1002/jclp.22681

Caribe, A. C., Studart, P., Bezerra-Filho, S., Brietzke, E., Nunes Noto, M., Vianna-Sulzbach, M., . . . Miranda-Scippa, A. (2015). Is religiosity a protective factor against suicidal behavior in bipolar I outpatients? *J Affect Disord, 186*, 156-161. doi:10.1016/j.jad.2015.07.024

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., . . . Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386-389. doi:10.1126/science.1083968

Castren, E., & Kojima, M. (2017). Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. *Neurobiol Dis, 97*(Pt B), 119-126. doi:10.1016/j.nbd.2016.07.010

Chang, W. C., Wong, C. S. M., Or, P. C. F., Chu, A. O. K., Hui, C. L. M., Chan, S. K. W., . . . Chen, E. Y. H. (2019). Inter-relationships among psychopathology, premorbid adjustment, cognition and psychosocial functioning in first-episode psychosis: a network analysis approach. *Psychol Med*, 1-9. doi:10.1017/S0033291719002113

Chen, Y., & VanderWeele, T. J. (2020). Spirituality, Religion and Suicide. In D. H. Rosmarin & H. Koenig (Eds.), *Handbook of Spirituality, Religion and Mental Health*. United Kingdom: Elseview.

Cho, Y., Lee, J. K., Kim, D. H., Park, J. H., Choi, M., Kim, H. J., . . . Park, Y. G. (2019). Factors associated with quality of life in patients with depression: A nationwide population-based study. *PLoS One, 14*(7), e0219455. doi:10.1371/journal.pone.0219455

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., . . . Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet, 391*(10128), 1357-1366. doi:10.1016/s0140-6736(17)32802-7

Cloninger, C. R. (2006). The science of well-being: an integrated approach to mental health and its disorders. *World Psychiatry, 5*.

Cook, C. C. H. (2011). The faith of the psychiatrist. *Mental Health, Religion & Culture, 14*(1), 9-17. doi:10.1080/13674671003622673

Corrêa, A. A. M., Moreira-Almeida, A., Menezes, P. R., Vallada, H., & Scazufca, M. (2011). Investigating the role played by social support in the association between religiosity and mental health in low income older adults: results from the São Paulo Ageing & Health Study (SPAH). *Braz J Psych, 33*.

Cramer, A. O., Van Borkulo, C. D., Giltay, E. J., Van der Maas, H. L., Kendler, K. S., Scheffer, M., & Borsboom, D. (2016). Major Depression as a Complex Dynamic System. *PLoS One, 11*(12), e0167490. doi:10.1371/journal.pone.0167490

Cuijpers, P., Donker, T., Weissman, M. M., Ravitz, P., & Cristea, I. A. (2016). Interpersonal Psychotherapy for Mental Health Problems: A Comprehensive Meta-Analysis. *Am J Psychiatry, 173*(7), 680-687. doi:10.1176/appi.ajp.2015.15091141

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: the NIMH Research Domain Criteria project. *Schizophr Bull, 36*(6), 1061-1062. doi:10.1093/schbul/sbq108

Dong, M., Zeng, L. N., Lu, L., Li, X. H., Ungvari, G. S., Ng, C. H., . . . Xiang, Y. T. (2019). Prevalence of suicide attempt in individuals with major depressive disorder: a meta-analysis of observational surveys. *Psychol Med, 49*(10), 1691-1704. doi:10.1017/S0033291718002301

DSM-5. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5* (Fifth Edition ed.): American Psychiatric Association.

Dunner, D. L., Rush, A. J., Russell, J. M., Burke, M., Woodard, S., Wingard, P., & Allen, J. (2006). Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry, 67*(5), 688-695. doi:10.4088/jcp.v67n0501

Eckhart, M. (1327). *The Complete Mystical Works of Meister Eckhart, Sermon Eighty-Three (2009)*. New York: The Crossroad Publishing Company.

Fazel, S., & Runeson, B. (2020). Suicide. *N Engl J Med, 382*(3), 266-274. doi:10.1056/NEJMra1902944

Fekadu, A., Donocik, J. G., & Cleare, A. J. (2018). Standardisation framework for the Maudsley staging method for treatment resistance in depression. *BMC Psychiatry, 18*(1), 100. doi:10.1186/s12888-018-1679-x

Fleck, M. P., Berlim, M. T., Lafer, B., Sougey, E. B., Porto, J. A., Brasil, M. A., . . . Hetem, L. A. (2009). Review of the guidelines of the Brazilian Medical Association for the tratment of depression (Full version). *Rev Bras Psiquiat., 31*, 7-17.

Fleck, M. P., Louzada, S., Xavier, M., Chachamovich, E., Vieira, G., Santos, L., & Pinzon, V. (2000). [Application of the Portuguese version of the abbreviated instrument of

quality life WHOQOL-bref]. *Rev Saude Publica, 34*(2), 178-183. doi:10.1590/s0034-89102000000200012

Fowler, J. W. (1981). *Stages of Faith: The Psychology of Human Development and the Quest for Meaning*: New York: Harper & Row.

Gagrani, M., Faiq, M. A., Sidhu, T., Dada, R., Yadav, R. K., Sihota, R., . . . Dada, T. (2018). Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: A randomized controlled trial. *Restor Neurol Neurosci, 36*(6), 741-753. doi:10.3233/RNN-180857

Gaynes, B. N., Warden, D., Trivedi, M. H., Wisniewski, S. R., Fava, M., & Rush, J. A. (2009). What did STAR-D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatric Services, 60*(11). doi:https://doi.org/10.1176/ps.2009.60.11.1439

Gradus, J. L., Rosellini, A. J., Horvath-Puho, E., Street, A. E., Galatzer-Levy, I., Jiang, T., . . . Sorensen, H. T. (2019). Prediction of Sex-Specific Suicide Risk Using Machine Learning and Single-Payer Health Care Registry Data From Denmark. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2019.2905

Grassi-Oliveira, R., Cogo-Moreira, H., Salum, G. A., Brietzke, E., Viola, T. W., Manfro, G. G., . . . Arteche, A. X. (2014). Childhood Trauma Questionnaire (CTQ) in Brazilian samples of different age groups: findings from confirmatory factor analysis. *PLoS One, 9*(1), e87118. doi:10.1371/journal.pone.0087118

Griep, R. H., Chor, D., Faerstein, E., Werneck, G. L., & Lopes, C. S. (2005). Construct validity of the Medical Outcomes Study's social support scale adapted to Portuguese in the Pró-Saúde Study. *Cad. Saúde Pública, 21*(3), 703-714. doi:doi: 10.1590/S0102-311X2005000300004

Gureje, O., Nortje, G., Makanjuola, V., Oladeji, B. D., Seedat, S., & Jenkins, R. (2015). The role of global traditional and complementary systems of medicine in the treatment of mental health disorders. *The Lancet Psychiatry, 2*(2), 168-177. doi:10.1016/s2215-0366(15)00013-9

Hackett, C., Grim, B. J., Cooperman, A., Ochoa, J. C., Gao, C., Shi, A. F., . . . Lugo, L. (2012). The Global Religious Landscape. A Report on the Size and Distribution of the World's Major Religious Groups as of 2010. *Pew Research Center*, 3-82. Retrieved from http://www.pewforum.org/global-religious-landscape.aspx

Hamilton, M. (1967). Development of a Rating Scale for Primary Depressive Illness. *Br J Soc Clin Psychol, 6*(4), 278-296. doi:DOI: 10.1111/j.2044-8260.1967.tb00530.x

Haslbeck, J. M. B., & Waldorp, L. J. (2019). mgm: Estimating Time-Varying Mixed Graphical Models in High-Dimensional Data. *Journal of Statistical Software, VV*(II), 1-49.

Herrman, H., Kieling, C., McGorry, P., Horton, R., Sargent, J., & Patel, V. (2018). Reducing the global burden of depression: a Lancet–World Psychiatric Association Commission. *The Lancet*. doi:10.1016/s0140-6736(18)32408-5

Heyland, D. K., Dodek, P., Rocker, G., Groll, D., Gafni, A., Pichora, D., . . . Canadian Researchers End-of-Life, N. (2006). What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *CMAJ, 174*(5), 627-633. doi:10.1503/cmaj.050626

Holvast, F., Burger, H., de Waal, M. M., van Marwijk, H. W., Comijs, H. C., & Verhaak, P. F. (2015). Loneliness is associated with poor prognosis in late-life depression: Longitudinal analysis of the Netherlands study of depression in older persons. *J Affect Disord, 185*, 1-7. doi:10.1016/j.jad.2015.06.036

Hosang, G. M., Shiles, C., Tansey, K. E., McGuffin, P., & Uher, R. (2014). Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. *BMC Med, 12*, 7. doi:10.1186/1741-7015-12-7

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, M., . . . McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci, 22*(3), 343-352. doi:10.1038/s41593-018-0326-7

Islam, M. R., Kabir, M. A., Ahmed, A., Kamal, A. R. M., Wang, H., & Ulhaq, A. (2018). Depression detection from social network data using machine learning techniques. *Health Inf Sci Syst, 6*(1), 8. doi:10.1007/s13755-018-0046-0

Jeste, D. V., Palmer, B. W., Rettew, D. C., & Boardman, S. (2015). Positive psychiatry: its time has come. *J Clin Psychiatry, 76*(6), 675-683. doi:10.4088/JCP.14nr09599

Kapczinski, N. S., Mwangi, B., Cassidy, R. M., Librenza-Garcia, D., Bermudez, M. B., Kauer-Sant'anna, M., . . . Passos, I. C. (2017). Neuroprogression and illness trajectories in bipolar disorder. *Expert Rev Neurother, 17*(3), 277-285. doi:10.1080/14737175.2017.1240615

Keller, M. B. (1992). Time to Recovery, Chronicity, and Levels of Psychopathology in Major Depression. *Archives of General Psychiatry, 49*(10). doi:10.1001/archpsyc.1992.01820100053010

Kendler, K. S. (2016). The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *Am J Psychiatry, 173*(8), 771-780. doi:10.1176/appi.ajp.2016.15121509

Kendler, K. S., Liu, X.-Q., Gardner, C. O., McCullough, M. E., Larson, D., & Prescott, C. A. (2003). Dimensions of Religiosity and Their Relationship to Lifetime Psychiatric and Substance Use Disorders. *American Journal of Psychiatry, 160*, 496-503.

Kendler, K. S., Thornton, L. M., & Gardner, C. O. (2001). Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. *Am J Psychiatry, 158*(4), 582-586. doi:10.1176/appi.ajp.158.4.582

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., . . . Group, C. D. W. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry, 61*(9), 540-560. doi:10.1177/0706743716659417

Kessler, R. C., & Bromet, E. J. (2013). The Epidemiology of Depression Across Cultures. *Annual Review of Public Health, 34*(1), 119-138. doi:10.1146/annurev-publhealth-031912-114409

King, M. B., & Koenig, H. G. (2009). Conceptualising spirituality for medical research and health service provision. *BMC Health Serv Res, 9*, 116. doi:10.1186/1472-6963-9-116

Kishi, T., Yoshimura, R., Ikuta, T., & Iwata, N. (2017). Brain-Derived Neurotrophic Factor and Major Depressive Disorder: Evidence from Meta-Analyses. *Front Psychiatry, 8*, 308. doi:10.3389/fpsyt.2017.00308

Koenig, H. G., Al-Zaben, F., & VanderWeele, T. J. (2020). Religion and psychiatry: recent developments in research. *BJPsych Advances*, 1-11. doi:10.1192/bja.2019.81

Koenig, H. G., Cohen, H. J., George, L. K., Hays, J. C., Larson, D. B., & Blazer, D. G. (1997). Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. *Int J Psychiatry Med, 27*(3), 233-250. doi:10.2190/40NF-Q9Y2-0GG7-4WH6

Koenig, H. G., George, L. K., & Peterson, B. L. (1998). Religiosity and Remission of Depression in Medically Ill Older Patients. *Am J Psychiatry, 155*(4), 536-542. doi:10.1176/ajp.155.4.536

Koenig, H. G., King, D. E., & Carson, V. B. (2012). *Handbook of Religion and Health*. New York, NY: Oxford University Press.

Koenig, H. G., Peteet, J. R., & VanderWeele, T. J. (2020). Religion and psychiatry: clinical applications. *BJPsych Advances*, 1-9. doi:10.1192/bja.2020.11

Koenig, H. G., Zaben, F. A., & Khalifa, D. A. (2012). Religion, spirituality and mental health in the West and the Middle East. *Asian J Psychiatr, 5*(2), 180-182. doi:10.1016/j.ajp.2012.04.004

Kowianski, P., Lietzau, G., Czuba, E., Waskow, M., Steliga, A., & Morys, J. (2018). BDNF: A Key Factor with Multipotent Impact on Brain Signaling and Synaptic Plasticity. *Cell Mol Neurobiol, 38*(3), 579-593. doi:10.1007/s10571-017-0510-4

Krause, N., Hill, P. C., Emmons, R., Pargament, K. I., & Ironson, G. (2016). Assessing the Relationship Between Religious Involvement and Health Behaviors. *Health Education & Behavior, 44*(2), 278-284. doi:10.1177/1090198116655314

Lawrence, R. E., Oquendo, M. A., & Stanley, B. (2016). Religion and Suicide Risk: A Systematic Review. *Arch Suicide Res, 20*(1), 1-21. doi:10.1080/13811118.2015.1004494

Lee, E., & Baumann, K. (2013). German psychiatrists' observation and interpretation of religiosity/spirituality. *Evid Based Complement Alternat Med, 2013*, 280168. doi:10.1155/2013/280168

Legge, R. M., Sendi, S., Cole, J. H., Cohen-Woods, S., Costafreda, S. G., Simmons, A., . . . Fu, C. H. (2015). Modulatory effects of brain-derived neurotrophic factor Val66Met polymorphism on prefrontal regions in major depressive disorder. *Br J Psychiatry, 206*(5), 379-384. doi:10.1192/bjp.bp.113.143529

Leskela, U., Rytsala, H., Komulainen, E., Melartin, T., Sokero, P., Lestela-Mielonen, P., & Isometsa, E. (2006). The influence of adversity and perceived social support on the outcome of major depressive disorder in subjects with different levels of depressive symptoms. *Psychol Med, 36*(6), 779-788. doi:10.1017/S0033291706007276

Li, S., Okereke, O. I., Chang, S.-C., Kawachi, I., & VanderWeele, T. J. (2016). Religious Service Attendance and Lower Depression Among Women—a Prospective Cohort Study. *Annals of Behavioral Medicine, 50*(6), 876-884. doi:10.1007/s12160-016-9813-9

Li, Y., Aggen, S., Shi, S., Gao, J., Li, Y., Tao, M., . . . Kendler, K. S. (2014). Subtypes of major depression: latent class analysis in depressed Han Chinese women. *Psychol Med, 44*(15), 3275-3288. doi:10.1017/S0033291714000749

Lim, C., Sim, K., Renjan, V., Sam, H. F., & Quah, S. L. (2014). Adapted cognitive-behavioral therapy for religious individuals with mental disorder: a systematic review. *Asian J Psychiatr, 9*, 3-12. doi:10.1016/j.ajp.2013.12.011

Lima, M. S., Soares, B. G., Paoliello, G., Machado Vieira, R., Martins, C. M., Mota Neto, J. I., . . . Volpe, F. M. (2007). The Portuguese version of the Clinical Global Impression-Schizophrenia Scale: validation study. *Braz J Psychiatry, 29*(3), 246-249. doi:10.1590/s1516-44462007000300010

Liu, Q., He, H., Yang, J., Feng, X., Zhao, F., & Lyu, J. (2019). Changes in the global burden of depression from 1990 to 2017: Findings from the Global Burden of Disease study. *J Psychiatr Res*. doi:10.1016/j.jpsychires.2019.08.002

Lomax, J. W., Kripal, J. J., & Pargament, K. I. (2011). Perspectives on “Sacred Moments” in Psychotherapy. *Am J Psychiatry, 168*.

Lucchetti, G., Lucchetti, A. L., & Vallada, H. (2013). Measuring spirituality and religiosity in clinical research: a systematic review of instruments available in the Portuguese language. *Sao Paulo Med J, 131*(2), 112-122. doi:10.1590/s1516-31802013000100022

Lutgendorf, S. K., Russell, D., Ullrich, P., Harris, T. B., & Wallace, R. (2004). Religious participation, interleukin-6, and mortality in older adults. *Health Psychol, 23*(5), 465-475. doi:10.1037/0278-6133.23.5.465

Malhi, G. S., & Mann, J. J. (2018). Depression. *The Lancet, 392*(10161), 2299-2312. doi:10.1016/s0140-6736(18)31948-2

Mastropieri, B., Schussel, L., Forbes, D., & Miller, L. (2015). Inner resources for survival: integrating interpersonal psychotherapy with spiritual visualization with homeless youth. *J Relig Health, 54*(3), 903-921. doi:10.1007/s10943-015-0044-3

McElroy, E., Napoleone, E., Wolpert, M., & Patalay, P. (2019). Structure and Connectivity of Depressive Symptom Networks Corresponding to Early Treatment Response. *EClinicalMedicine, 8*, 29-36. doi:10.1016/j.eclinm.2019.02.009

Menegatti-Chequini, M. C., Goncalves, J. P., Leao, F. C., Peres, M. F., & Vallada, H. (2016). A preliminary survey on the religious profile of Brazilian psychiatrists and their approach to patients' religiosity in clinical practice. *BJPsych Open, 2*(6), 346-352. doi:10.1192/bjpo.bp.116.002816

Miller, L., Bansal, R., Wickramaratne, P., Hao, X., Tenke, C. E., Weissman, M. M., & Peterson, B. S. (2014). Neuroanatomical correlates of religiosity and spirituality: a study in adults at high and low familial risk for depression. *JAMA Psychiatry, 71*(2), 128-135. doi:10.1001/jamapsychiatry.2013.3067

Miller, L., Wickramaratne, P., Gameroff, M. J., Sage, M., Tenke, C. E., & Weissman, M. M. (2012). Religiosity and major depression in adults at high risk: a ten-year prospective study. *Am J Psychiatry, 169*(1), 89-94. doi:10.1176/appi.ajp.2011.10121823

Molendijk, M. L., Spinhoven, P., Polak, M., Bus, B. A., Penninx, B. W., & Elzinga, B. M. (2014). Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N=9484). *Mol Psychiatry, 19*(7), 791-800. doi:10.1038/mp.2013.105

Moreira-Almeida, A., Koenig, H. G., & Lucchetti, G. (2014). Clinical implications of spirituality to mental health: review of evidence and practical guidelines. *Revista Brasileira de Psiquiatria, 36*(2), 176-182. doi:10.1590/1516-4446-2013-1255

Moreira-Almeida, A., & Lotufo Neto, F. (2005). Spiritist views of mental disorders in Brazil. *Transcult Psychiatry, 42*(4), 570-595. doi:10.1177/1363461505058916

Moreira-Almeida, A., Neto, F. L., & Koenig, H. G. (2006). Religiousness and mental health: a review. *Rev Bras Psiquiat., 28*, 242-250.

Moreira-Almeida, A., Pinsky, I., Zaleski, M., & Laranjeira, R. (2010). Religious involvement and sociodemographic factors: a Brazilian national survey. *Rev Psiq. Clín., 37*, 12-15.

Moreira-Almeida, A., Sharma, A., van Rensburg, B. J., Verhagen, P. J., & Cook, C. C. (2016). WPA Position Statement on Spirituality and Religion in Psychiatry. *World Psychiatry, 15*(1), 87-88. doi:10.1002/wps.20304

Moreira-Almeida, A., Sharma, A., van Rensburg, B. J., Verhagen, P. J., & Cook, C. C. H. (2016). WPA Position Statement on Spirituality and Religion in Psychiatry. *World Psychiatry, 15*(1), 87-88. doi:10.1002/wps.20304

Mosqueiro, B. P., da Rocha, N. S., & Fleck, M. P. d. A. (2015). Intrinsic religiosity, resilience, quality of life, and suicide risk in depressed inpatients. *J Affect Disord, 179*, 128-133. doi:10.1016/j.jad.2015.03.022

Mosqueiro, B. P., Rezende, A., & Moreira-Almeida, A. (2020). Spirituality, Religiosity and Mood Disorders. In D. H. Rosmarin & H. G. Koenig (Eds.), *Handbook of Spirituality, Religion, and Mental Health* (Vol. 1). United Kingdom: Elsevier.

Murray, C. J. L., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., . . . Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2197-2223. doi:10.1016/s0140-6736(12)61689-4

Na, K. S., Won, E., Kang, J., Chang, H. S., Yoon, H. K., Tae, W. S., . . . Ham, B. J. (2016). Brain-derived neurotrophic factor promoter methylation and cortical thickness in recurrent major depressive disorder. *Sci Rep, 6*, 21089. doi:10.1038/srep21089

Ormel, J., Hartman, C. A., & Snieder, H. (2019). The genetics of depression: successful genome-wide association studies introduce new challenges. *Transl Psychiatry, 9*(1), 114. doi:10.1038/s41398-019-0450-5

Panzini, R. G., Maganha, C., Rocha, N. S., Bandeira, D. R., & Fleck, M. P. (2011). Brazilian validation of the Quality of Life Instrument/spirituality, religion and personal beliefs. *Rev Saude Publica, 45*(1), 153-165.

Panzini, R. G., Mosqueiro, B. P., Zimpel, R. R., Bandeira, D. R., Rocha, N. S., & Fleck, M. P. (2017). Quality-of-life and spirituality. *Int Rev Psychiatry, 29*(3), 263-282. doi:10.1080/09540261.2017.1285553

Pargament, K. I., Koenig, H. G., & Perez, L. M. (2000). The many methods of religious coping: development and initial validation of the RCOPE. *J Clin Psychol, 56*, 519-543.

Pargament, K. I., & Lomax, J. W. (2013). Understanding and addressing religion among people with mental illness. *World Psychiatry, 12*(1), 26-32. doi:10.1002/wps.20005

Pargament, K. I., Murray-Swank, N., Magyar, G. M., & Ano, G. G. (2005). Spiritual struggle: A phenomenon of interest to psychology and religion. In W. R. Miller & H. Delaney (Eds.), *Judeo-Christian perspectives on psychology: Human nature, motivation, and change* (pp. 245–268). Washington, DC: APA Books.

Pargament, K. I., Zinnbauer, B. J., Scott, A. B., Butter, E. M., Zerowin, J., & Stanik, P. (1998). Red Flags and Religious Coping: Identifying Some Religious Warning Signs Among People in Crisis. *J Clin Psychol, 54*, 77-89. doi:CCC 0021-9762/98/010077-13

Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., . . . Whiteford, H. (2016). Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *The Lancet, 387*(10028), 1672-1685. doi:10.1016/s0140-6736(15)00390-6

Paterniti, S., Sterner, I., Caldwell, C., & Bisserbe, J. C. (2017). Childhood neglect predicts the course of major depression in a tertiary care sample: a follow-up study. *BMC Psychiatry, 17*(1), 113. doi:10.1186/s12888-017-1270-x

Pena, C. J., & Nestler, E. J. (2018). Progress in Epigenetics of Depression. *Prog Mol Biol Transl Sci, 157*, 41-66. doi:10.1016/bs.pmbts.2017.12.011

Peteet, J. R. (2012). Spiritually integrated treatment of depression: a conceptual framework. *Depress Res Treat, 2012*, 124370. doi:10.1155/2012/124370

Peterson, R. E., Cai, N., Dahl, A. W., Bigdeli, T. B., Edwards, A. C., Webb, B. T., . . . Kendler, K. S. (2018). Molecular Genetic Analysis Subdivided by Adversity Exposure Suggests

Etiologic Heterogeneity in Major Depression. *American Journal of Psychiatry, 175*(6), 545-554. doi:10.1176/appi.ajp.2017.17060621

Polyakova, M., Stuke, K., Schuemberg, K., Mueller, K., Schoenknecht, P., & Schroeter, M. L. (2015). BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. *J Affect Disord, 174*, 432-440. doi:10.1016/j.jad.2014.11.044

Richards, D. (2011). Prevalence and clinical course of depression: a review. *Clinical Psychology Review, 31*, 1117-1125. doi:10.1016/j.cpr.2011.07.004

Rim, J. I., Ojeda, J. C., Svob, C., Kayser, J., Drews, E., Kim, Y., . . . Weissman, M. M. (2019). Current Understanding of Religion, Spirituality, and Their Neurobiological Correlates. *Harv Rev Psychiatry, 27*(5), 303-316. doi:10.1097/HRP.0000000000000232

Rodrigues, C. D., de Souza, D. S., Rodrigues, H. M., & Konstantyner, T. (2019). Trends in suicide rates in Brazil from 1997 to 2015. *Braz J Psychiatry, 41*(5), 380-388. doi:10.1590/1516-4446-2018-0230

Rosmarin, D. H., Forester, B. P., Shassian, D. M., Webb, C. A., & Bjorgvinsson, T. (2015). Interest in spiritually integrated psychotherapy among acute psychiatric patients. *J Consult Clin Psychol, 83*(6), 1149-1153. doi:10.1037/ccp0000046

Rosmarin, D. H., Malloy, M. C., & Forester, B. P. (2014). Spiritual struggle and affective symptoms among geriatric mood disordered patients. *Int J Geriatr Psychiatry, 29*(6), 653-660. doi:10.1002/gps.4052

Rosmarin, D. H., Moreira-Almeida, A., & Koenig, H. (2018). Religion and psychotic experiences. *Acta Psychiatr Scand, 138*(2), 173. doi:10.1111/acps.12917

Rosmarin, D. H., Pargament, K. I., & Koenig, H. G. (2020). Spirituality and mental health: challenges and opportunities. *Lancet Psychiatry*. doi:10.1016/S2215-0366(20)30048-1

Salvi, F., Miller, M. D., Grilli, A., Giorgi, R., Towers, A. L., Morichi, V., . . . Dessi-Fulgheri, P. (2008). A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc, 56*(10), 1926-1931. doi:10.1111/j.1532-5415.2008.01935.x

Schuch, F. B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P. B., Silva, E. S., . . . Stubbs, B. (2018). Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. *Am J Psychiatry, 175*(7), 631-648. doi:10.1176/appi.ajp.2018.17111194

Seo, J. S., Wei, J., Qin, L., Kim, Y., Yan, Z., & Greengard, P. (2017). Cellular and molecular basis for stress-induced depression. *Mol Psychiatry, 22*(10), 1440-1447. doi:10.1038/mp.2016.118

Shimada, H., Makizako, H., Doi, T., Yoshida, D., Tsutsumimoto, K., Anan, Y., . . . Suzuki, T. (2014). A Large, Cross-Sectional Observational Study of Serum BDNF, Cognitive Function, and Mild Cognitive Impairment in the Elderly. *Frontiers in Aging Neuroscience, 6*. doi:10.3389/fnagi.2014.00069

Silva, M. T., Galvao, T. F., Martins, S. S., & Pereira, M. G. (2014). Prevalence of depression morbidity among Brazilian adults: a systematic review and meta-analysis. *Braz J Psychiatry, 36*(3), 262-270. doi:10.1590/1516-4446-2013-1294

Silveira, D. R., & Mahfoud, M. (2008). Viktor Emil Frankl's contribution to the concept of resilience. *Estudos de Psicologia, 25*, 567-576.

Skevington, S. M., Gunson, K. S., & O'Connell, K. A. (2013). Introducing the WHOQOL-SRPB BREF: developing a short-form instrument for assessing spiritual, religious and

personal beliefs within quality of life. *Qual Life Res, 22*(5), 1073-1083. doi:10.1007/s11136-012-0237-0

Smith, T. B., McCullough, M. E., & Poll, J. (2003). Religiousness and depression: Evidence for a main effect and the moderating influence of stressful life events. *Psychological Bulletin, 129*(4), 614-636. doi:10.1037/0033-2909.129.4.614

Snaith, N., Schultz, T., Proeve, M., & Rasmussen, P. (2018). Mindfulness, self-compassion, anxiety and depression measures in South Australian yoga participants: implications for designing a yoga intervention. *Complement Ther Clin Pract, 32*, 92-99. doi:10.1016/j.ctcp.2018.05.009

Souza, L. H., Salum, G. A., Mosqueiro, B. P., Caldieraro, M. A., Guerra, T. A., & Fleck, M. P. (2016). Interpersonal psychotherapy as add-on for treatment-resistant depression: A pragmatic randomized controlled trial. *J Affect Disord, 193*, 373-380. doi:10.1016/j.jad.2016.01.004

Spanemberg, L., Salum, G. A., Caldieraro, M. A., Vares, E. A., Tiecher, R. D., da Rocha, N. S., . . . Fleck, M. P. (2014). Personality styles in depression: Testing reliability and validity of hierarchically organized constructs. *Personality and Individual Differences, 70*, 72-79. doi:10.1016/j.paid.2014.06.021

Stroppa, A., & Moreira-Almeida, A. (2013). Religiosity, mood symptoms, and quality of life in bipolar disorder. *Bipolar Disord, 15*(4), 385-393. doi:10.1111/bdi.12069

Svob, C., Wang, Z., Weissman, M. M., Wickramaratne, P., & Posner, J. (2016). Religious and spiritual importance moderate relation between default mode network connectivity and familial risk for depression. *Neuroscience Letters, 634*, 94-97. doi:10.1016/j.neulet.2016.10.009

Svob, C., Wong, L. Y. X., Gameroff, M. J., Wickramaratne, P. J., Weissman, M. M., & Kayser, J. (2019). Understanding self-reported importance of religion/spirituality in a North American sample of individuals at risk for familial depression: A principal component analysis. *PLoS One, 14*(10), e0224141. doi:10.1371/journal.pone.0224141

Taunay, T. C. D., Gondim, F. d. A. A., Macedo, D. S., Moreira-Almeida, A., Gurgel, L. d. A., Andrade, L. M. S., & Carvalho, A. F. (2012). Validity of the Brazilian version of the Duke Religion Index (DUREL). *Rev Psiq. Clín., 39*, 130-135.

Tsankova, N. M., Berton, O., Renthal, W., Kumar, A., Neve, R. L., & Nestler, E. J. (2006). Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci, 9*(4), 519-525. doi:10.1038/nn1659

Tsuang, M. T., Williams, W. M., Simpson, J. C., & Lyons, M. J. (2002). Pilot study of spirituality and mental health in twins. *Am J Psychiatry, 159*(3), 486-488. doi:10.1176/appi.ajp.159.3.486

Ungar, M., & Theron, L. (2020). Resilience and mental health: how multisystemic processes contribute to positive outcomes. *The Lancet Psychiatry, 7*(5), 441-448. doi:10.1016/s2215-0366(19)30434-1

Vaillant, G. E. (2013). Psychiatry, religion, positive emotions and spirituality. *Asian J Psychiatr, 6*(6), 590-594. doi:10.1016/j.ajp.2013.08.073

Van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B. W., Waldorp, L. J., & Schoevers, R. A. (2015). Association of Symptom Network Structure With the Course of Depression. *JAMA Psychiatry, 72*(12), 1219-1226. doi:10.1001/jamapsychiatry.2015.2079

Van den Brink, R. H. S., Schutter, N., Hanssen, D. J. C., Elzinga, B. M., Rabeling-Keus, I. M., Stek, M. L., . . . Oude Voshaar, R. C. (2018). Prognostic significance of social network,

social support and loneliness for course of major depressive disorder in adulthood and old age. *Epidemiol Psychiatr Sci, 27*(3), 266-277. doi:10.1017/S2045796017000014

VanderWeele, T. J., Balboni, T. A., & Koh, H. K. (2017). Health and Spirituality. *JAMA, 318*(6), 519-520. doi:10.1001/jama.2017.8136

VanderWeele, T. J., Li, S., Tsai, A. C., & Kawachi, I. (2016). Association Between Religious Service Attendance and Lower Suicide Rates Among US Women. *JAMA Psychiatry, 73*(8), 845-851. doi:10.1001/jamapsychiatry.2016.1243

VanderWeele, T. J., McNeely, E., & Koh, H. K. (2019). Reimagining Health-Flourishing. *JAMA, 321*(17), 1667-1668. doi:10.1001/jama.2019.3035

Vares, E. A., Salum, G. A., Spanemberg, L., Caldieraro, M. A., & Fleck, M. P. (2015). Depression Dimensions: Integrating Clinical Signs and Symptoms from the Perspectives of Clinicians and Patients. *PLoS One, 10*(8), e0136037. doi:10.1371/journal.pone.0136037

Verduijn, J., Verhoeven, J. E., Milaneschi, Y., Schoevers, R. A., van Hemert, A. M., Beekman, A. T. F., & Penninx, B. (2017). Reconsidering the prognosis of major depressive disorder across diagnostic boundaries: full recovery is the exception rather than the rule. *BMC Med, 15*(1), 215. doi:10.1186/s12916-017-0972-8

Wagnild, G. M. (2014). *The Resilience Scale User's Guide* (P. E. Guinn Ed.). Montana, United States of America: Resilience Center.

Wang, L., Koenig, H. G., He, Z., Sun, X., Shohaib, S. A., & Wang, Z. (2019). Religiosity and Telomere Length: Moderating Effect of Religiosity on the Relationship Between High-Risk Polymorphisms of the Apolipoprotein E and TOMM40 Gene and Telomere Length. *J Appl Gerontol*, 733464819865415. doi:10.1177/0733464819865415

Willard, A. K., & Norenzayan, A. (2017). "Spiritual but not religious": Cognition, schizotypy, and conversion in alternative beliefs. *Cognition, 165*, 137-146. doi:10.1016/j.cognition.2017.05.018

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., . . . Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord, 20*(2), 97-170. doi:10.1111/bdi.12609

Zimpel, R. R., Panzini, R. G., Bandeira, D. R., Fleck, M. P., & da Rocha, N. S. (2019). Psychometric properties of the WHOQOL-SRPB BREF, Brazilian Portuguese version. *Braz J Psychiatry, 41*(5), 411-418. doi:10.1590/1516-4446-2018-0083

12. ANEXOS

12.1. Questionário sobre Religiosidade/Espiritualidade

1. Você possui alguma denominação religiosa?

1. ( ) Católico 2. ( ) Evangélico 3. ( ) Espírita 4. ( ) Religiões Afro-brasileiras
5. ( ) Budista 6. ( ) Islamismo 7. ( ) Judaica 8. ( ) Sem religião, com espiritualidade
9. ( ) Agnóstico 10. ( ) Ateísta 11. ( )
Outra_____

2. Frequenta mais de uma religião?

( ) 1. Sim. Especificar _____
( ) 2. Não.

3. Você acha importante os profissionais de saúde perguntarem sobre a religiosidade e espiritualidade nos atendimentos em saúde?

( ) 1. Sim
( ) 2. Não

4. Algum profissional da área da saúde já perguntou sobre sua religiosidade ou espiritualidade em seus atendimentos em saúde?

( ) 1. Sim. Se sim:
a) Foi perguntado aqui no Hospital de Clínicas? ( ) 1. Sim ( ) 2. Não
b) Foi perguntado por algum médico psiquiatra? ( ) 1. Sim ( ) 2. Não
( ) 2. Não.

5. Você gostaria de participar de uma terapia que integrasse aspectos ligados a religiosidade/espiritualidade diretamente no seu tratamento?

( ) 1. Sim
( ) 2. Não

6. Você acredita que sua religião pode ser contra seu tratamento para depressão (por exemplo, uso de medicações)?

( ) 1. Sim
( ) 2. Não

7. Selecione três fatores que na sua opinião mais podem contribuir na melhora da sua depressão.

( ) a) Apoio da família
( ) b) Melhora na situação financeira
( ) c) Melhora no trabalho
( ) d) Melhora na saúde
( ) e) Conversar sobre meus problemas
( ) f) Uso de Medicações
( ) g) Religiosidade/Espiritualidade
( ) h) Exercício físico
( ) i) Outros_____

12.2. Escala de Religiosidade de Duke (DUREL)

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1. Com que frequência você vai a uma igreja, templo ou outro encontro religioso?

1. Mais do que uma vez por semana
2. Uma vez por semana
3. Duas a três vezes por mês
4. Algumas vezes por ano
5. Uma vez por ano ou menos
6. Nunca

2. Com que frequência você dedica o seu tempo a atividades religiosas individuais, como preces, rezas, meditações, leitura da bíblia ou de outros textos religiosos?

1. Mais do que uma vez ao dia
2. Diariamente
3. Duas ou mais vezes por semana
4. Uma vez por semana
5. Poucas vezes por mês
6. Raramente ou nunca

A seção seguinte contém 3 frases a respeito de crenças ou experiências religiosas. Por favor, anote o quanto cada frase se aplica a você.

3. Em minha vida, eu sinto a presença de Deus (ou do Espírito Santo).

1. Totalmente verdade para mim
2. Em geral é verdade
3. Não estou certo
4. Em geral não é verdade
5. Não é verdade

4. As minhas crenças religiosas estão realmente por trás de toda a minha maneira de viver.

1. Totalmente verdade para mim
2. Em geral é verdade
3. Não estou certo
4. Em geral não é verdade
5. Não é verdade

5. Eu me esforço muito para viver a minha religião em todos os aspectos da vida.

1. Totalmente verdade para mim
2. Em geral é verdade
3. Não estou certo
4. Em geral não é verdade
5. Não é verdade

12.3. Escala WHOQOL-SRPB Versão Abreviada

As seguintes perguntas indagam a respeito das suas crenças espirituais, religiosas ou pessoais, e como essas crenças afetaram a sua qualidade de vida. Estas perguntas são planejadas para serem aplicáveis a pessoas com origem em muitas culturas diferentes, com uma variedade de crenças espirituais, religiosas ou pessoais. Se você acredita em determinada religião, como por exemplo o Judaísmo, Cristianismo, Islamismo ou Budismo, você provavelmente responderá às perguntas a seguir lembrando-se das suas crenças religiosas. Se não seguir a uma religião específica, mas ainda acredita que existe algo mais elevado e mais poderoso além do mundo físico e material, você poderá responder às perguntas que seguem a partir desta perspectiva. Por exemplo, você pode acreditar em uma força espiritual superior ou no poder curativo da Natureza. Por outro lado, você talvez não acredite em uma entidade espiritual superior, mas poderá ter crenças pessoais fortes ou algo que segue, como, por exemplo, acreditar em uma teoria científica, um modo de vida pessoal, uma determinada filosofia ou código moral e ético.

Quando em algumas perguntas forem utilizadas palavras como espiritualidade, por favor, responda em termos de seu próprio sistema de crença pessoal, seja ele religioso, espiritual ou pessoal. As perguntas a seguir indagam como as suas crenças afetaram diversos aspectos da sua qualidade de vida nas últimas duas semanas. Por exemplo, uma pergunta é : “Até que ponto você se sente ligado à sua mente corpo e alma? Se você tiver vivenciado muito isso, faça um círculo em torno do número abaixo de “muito ”. Se não tiver vivenciado isto em nenhum momento, faça um círculo em trono do número abaixo de “nada”. Você deve fazer um círculo em torno de um dos números no meio, se desejar indicar que a sua resposta está em algum ponto entre “Nada” e “Muito”. As perguntas referem-se às últimas duas semanas.

1.1. Até que ponto alguma conexão com um ser espiritual ajuda você a passar por épocas difíceis?
1 Nada
2 Muito pouco
3 Mais ou menos
4 Bastante
5 Extremamente

2.3. Até que ponto você sente que sua vida tem uma finalidade?
1 Nada
2 Muito pouco
3 Mais ou menos
4 Bastante
5 Extremamente

8.2. Até que ponto a fé lhe dá conforto no dia-a-dia?
1 Nada
2 Muito pouco
3 Mais ou menos
4 Bastante
5 Extremamente

7.2. Até que ponto você está esperançoso com sua vida?
1 Nada
2 Muito pouco
3 Mais ou menos
4 Bastante
5 Extremamente

SP3.1. Até que ponto você consegue ter admiração pelas coisas ao seu redor? (p. ex., natureza, arte, música)
1. Nada
2. Muito pouco
3. Médio
4. Muito
5. Completamente

SP5.3. O quanto a força espiritual o ajuda a viver melhor?
1. Nada
2. Muito pouco
3. Médio
4. Muito
5. Completamente

SP6.2. Até que ponto você sente paz interior?
1. Nada
2. Muito pouco
3. Médio
4. Muito
5. Completamente

SP4.2. Quão satisfeito você está por ter um equilíbrio entre a mente, o corpo e a alma?
1. Muito insatisfeito
2. Insatisfeito
3. Nem satisfeito nem insatisfeito
4. Satisfeito
5. Muito satisfeito

12.4. Questionário de Apoio Social (MOS)

As próximas perguntas são sobre aspectos da sua vida com a família e amigos na sua vida pessoal e oportunidades em que as pessoas procuram por outras em busca de companhia, ajuda ou outros tipos de apoio.

I1. Com quantos PARENTES você se sente à vontade e pode falar sobre quase tudo? (Se for o caso, inclua esposo(a), companheiro(a) ou filhos nesta resposta)

_____ parentes ☐ não tenho nenhum parente

I2.Com quantos AMIGOS você se sente à vontade e pode falar sobre quase tudo? (Não inclua nesta resposta esposo (a), companheiro (a), filhos ou outros parentes)

_____ amigos ☐ não tenho nenhum amigo

I3. Se você precisar, com que frequência você conta com alguém:	**Nunca**	Raramente	**Às vezes**	**Quase Sempre**	**Sempre**
a) Que o ajude se você ficar de cama?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b) Para lhe ouvir quando você precisa falar?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c) Para lhe dar bons conselhos em uma situação de crise?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d) Para levá-lo ao médico?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e) Que demonstre amor e afeto por você?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
f) Para divertirem-se juntos?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
g) Para lhe dar informação que o ajude a compreender determinada situação?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
h) Em quem confiar ou para falar de você ou sobre seus problemas?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
i) Que lhe dê um abraço?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
j) Com quem relaxar?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
l) Para preparar suas refeições se você não puder prepará-las?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
m) De quem realmente quer conselhos?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
n) Com quem distrair a cabeça?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

I3. Se você precisar, com que frequência você conta com alguém:	**Nunca**	Raramente	**Às vezes**	**Quase Sempre**	**Sempre**
o) Para ajudá-lo nas tarefas diárias se você ficar doente?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
p) Para compartilhar seus medos e preocupações mais íntimos?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
q) Para dar sugestão sobre como lidar com um problema pessoal?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
r) Para fazer coisas agradáveis?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
s) Que compreenda seus problemas?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
t) Que você ame e faça você se sentir querido?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

12.5. Escala de Resiliência de 14 Itens (RS-14)

(versão reduzida de Gail Wagnild & Heather Young, 1993, adaptada por Pesce, 2005)

Por favor para cada uma das questões que se seguem, coloque um círculo à volta do número que melhor corresponde ao seu grau de concordância relativamente a cada uma das seguintes afirmações:

	DISCORDO			NEM CONCORDO NEM DISCORDO	´CONCORDO		
	Totalmente	Muito	Pouco		Pouco	Muito	Totalmente
2. Eu costumo lidar com os problemas de uma forma ou de outra.	1	2	3	4	5	6	7
6. Eu sinto orgulho de ter realizado coisas em minha vida.	1	2	3	4	5	6	7
7. Eu costumo aceitar as coisas sem muita preocupação.	1	2	3	4	5	6	7
8. Eu sou amigo de mim mesmo.	1	2	3	4	5	6	7
9. Eu sinto que posso lidar com várias coisas ao mesmo tempo.	1	2	3	4	5	6	7
10. Eu sou determinado.	1	2	3	4	5	6	7
13. Eu posso enfrentar tempos difíceis porque já experimentei dificuldades antes.	1	2	3	4	5	6	7
14. Eu sou disciplinado.	1	2	3	4	5	6	7
15. Eu mantenho interesse nas coisas.	1	2	3	4	5	6	7
16. Eu normalmente posso achar motivo para rir.	1	2	3	4	5	6	7
17. Minha crença em mim mesmo me leva a atravessar tempos difíceis.	1	2	3	4	5	6	7
18. Em uma emergência, eu sou uma pessoa em quem as pessoas podem contar.	1	2	3	4	5	6	7
21. Minha vida tem sentido.	1	2	3	4	5	6	7
23. Quando eu estou numa situação difícil, eu normalmente acho um saída.	1	2	3	4	5	6	7

12.6. Escala de Maudsley

Parâmetros	Especificação	Pontuação
1. Duração	Agudo (<12 meses)	1
	Subagudo (13-24 meses)	2
	Crônico (>24 meses)	3
2. Gravidade dos Sintomas (baseline)	Subsindrômicos	1
	Leves	2
	Moderados	3
	Grave sem Psicose	4
	Grave com Psicose	5
3. Falha de Antidepressivos	Nível 1: 1-2 antidepressivos	1
	Nível 2: 3-4 medicações	2
	Nível 3: 5-6 medicações	3
	Nível 4: 7-10 medicações	4
	Nível 5: >10 medicações	5
4. Potencialização	Não usou	0
	Usou	1
5. ECT	Não usou	0
	Usou	1
6. Total		

12.7. Participações em Publicações Científicas Relacionadas a Tese de Doutorado

12.7.1. Publicação em Anais de Evento Científico Internacional

(1) Interest in religion, spirituality and spiritually integrated psychotherapy among Brazilian depressed patients. Bruno Paz Mosqueiro, Mateus Messinger, Felipe Bauer, William Barcelos, Mariana Uequed, Gabriela Possebom, Marco Antonio Caldieraro, Marcelo Pio de Almeida Fleck. ICPM Abstracts. Psychother Psychosom 2019. 88 Sup. 1 (p. 89-90). International College of Psychosomatic Medicine World Congress. Florence. Italy, 2019.

12.7.2. Publicações de Artigos Científicos

(1) Quality-**of**-**life** and **spirituality**.
Panzini RG, Mosqueiro BP, Zimpel RR, Bandeira DR, Rocha NS, Fleck MP.Int Rev Psychiatry. 2017 Jun;29(3):263-282. doi: 10.1080/09540261.2017.1285553.PMID: 28587554 Review.

(2) Espiritualidade e Resiliência na Atenção Domiciliar.
Zandavalli, R.B.; Santos, D.T.; Silveira, J.; Bueno, R.M.; de Castro Filho, E.D.; Mosqueiro, B.P.
Revista Brasileira de Medicina de Família e Comunidade.
Manuscript accepted for publication. 2020.

(3) Religiosity/spirituality, motivation and self-efficacy in the treatment of crack users.
Ely, A.; Mosqueiro, B.P. *Archives of Clinical Psychiatry.*
Manuscript submitted for publication. 2020.

(4) Perceived Barriers, Benefits and Correlates of Physical Activity in Outpatients with Major Depressive Disorder: a study from Brazil.
Monteiro, F. Schuch, F., Deslandes, A. Vancampfort, D. Mosqueiro, B.P., Messinger, M.F., Caldieraro, M., Fleck, M.P. Psychiatric Research 284 (2020) 112751.

12.7.3. Participações em Livros Acadêmicos

(1) Chapter Handbook of Spirituality, Religion and Mental Health. Elsevier, 2020.
Editors: David H. Rosmarin, Harold Koenig.
Authors: Mosqueiro, B.P.; Rezende, A.; Moreira-Almeida, A;
Chapter 1: *Spirituality, Religion and Mood Disorders.*

(2) Book Spirituality and Mental Health Across Cultures. Oxford University Press Book. 2020 Editors: Alexander Moreira-Almeida, Bruno Paz Mosqueiro, Dinesh Bhugra
In preparation. 2020.

12.8. Participações em Eventos e Atividades Científicas

2016
Congresso Brasileiro de Psiquiatria São Paulo, Brasil
Mesa-Redonda: Psicoterapia de Orientação Analítica e Espiritualidade

2017
Congresso Mundial de Psiquiatria Berlim, Alemanha.
Apresentação oral: Religiosity and Clinical Outcomes of Depressed Inpatients in South Brazil

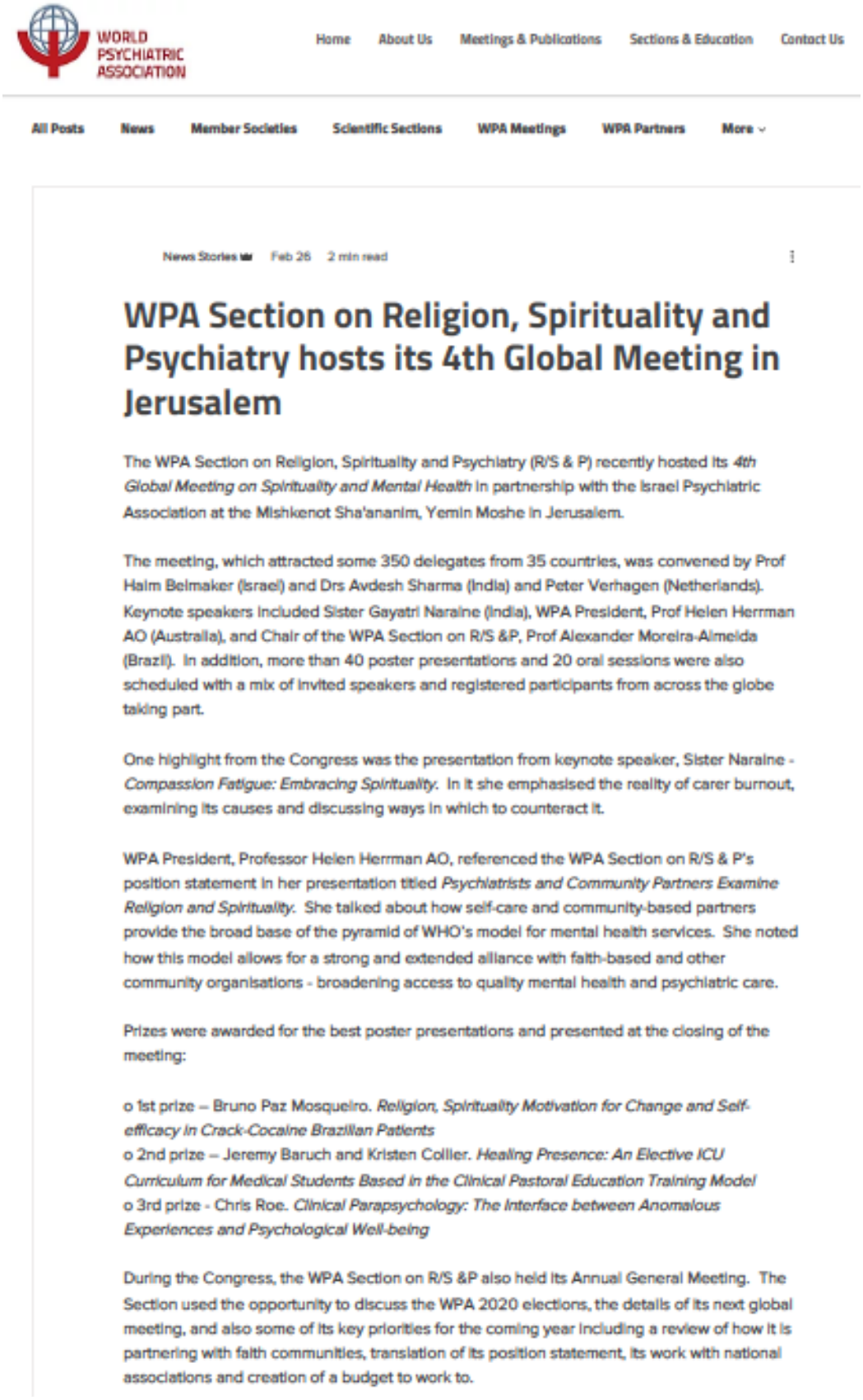
2017
Congresso Brasileiro de Psiquiatria. São Paulo, Brasil.
Curso: Pesquisando o Impacto da Religiosidade e Espiritualidade em Saúde Mental

2019
Cresso Brasileiro de Psiquiatria. Rio de Janeiro.
Curso: Psicoterapia e Espiritualidade

2019
Ciclo de Avanços em Psiquiatria APRS.
Apresentação oral: Human Flourishing e Espiritualidade: Contribuições para a Psiquiatria

2019
4th Global Meeting in Spirituality and Mental Health. WPA. Jerusalém. Israel.
Apresentação oral como convidado: Resilience, Depression and Spirituality

12.9. Premiação em Evento Internacional sobre Psiquiatria e Espiritualidade 2019



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WPA Section on Religion, Spirituality and Psychiatry hosts its 4th Global Meeting in Jerusalem

The WPA Section on Religion, Spirituality and Psychiatry (R/S & P) recently hosted its *4th Global Meeting on Spirituality and Mental Health* in partnership with the Israel Psychiatric Association at the Mishkenot Sha'ananim, Yemin Moshe in Jerusalem.

The meeting, which attracted some 350 delegates from 35 countries, was convened by Prof Haim Belmaker (Israel) and Drs Avdesh Sharma (India) and Peter Verhagen (Netherlands). Keynote speakers included Sister Gayatri Naraine (India), WPA President, Prof Helen Herrman AO (Australia), and Chair of the WPA Section on R/S &P, Prof Alexander Moreira-Almeida (Brazil). In addition, more than 40 poster presentations and 20 oral sessions were also scheduled with a mix of invited speakers and registered participants from across the globe taking part.

One highlight from the Congress was the presentation from keynote speaker, Sister Naraine - *Compassion Fatigue: Embracing Spirituality*. In it she emphasised the reality of carer burnout, examining its causes and discussing ways in which to counteract it.

WPA President, Professor Helen Herrman AO, referenced the WPA Section on R/S & P's position statement in her presentation titled *Psychiatrists and Community Partners Examine Religion and Spirituality*. She talked about how self-care and community-based partners provide the broad base of the pyramid of WHO's model for mental health services. She noted how this model allows for a strong and extended alliance with faith-based and other community organisations - broadening access to quality mental health and psychiatric care.

Prizes were awarded for the best poster presentations and presented at the closing of the meeting:

o 1st prize – Bruno Paz Mosqueiro. *Religion, Spirituality Motivation for Change and Self-efficacy in Crack-Cocaine Brazilian Patients*
o 2nd prize – Jeremy Baruch and Kristen Collier. *Healing Presence: An Elective ICU Curriculum for Medical Students Based in the Clinical Pastoral Education Training Model*
o 3rd prize - Chris Roe. *Clinical Parapsychology: The Interface between Anomalous Experiences and Psychological Well-being*

During the Congress, the WPA Section on R/S &P also held its Annual General Meeting. The Section used the opportunity to discuss the WPA 2020 elections, the details of its next global meeting, and also some of its key priorities for the coming year including a review of how it is partnering with faith communities, translation of its position statement, its work with national associations and creation of a budget to work to.

12.10. Participação em Iniciativas de Estudo e Pesquisa sobre Espiritualidade

(1) Núcleo de Psiquiatria e Espiritualidade da Associação de Psiquiatria do Rio Grande do Sul (NUPE-APRS)
Membro ativo entre 2013 e 2019.

(2) Departamento de Psiquiatria e Espiritualidade da Associação de Psiquiatria do Rio Grande do Sul (DPE-APRS)
Diretor científico de 2019 e 2020.

(3) Seção de Estudos e Pesquisas em Espiritualidade e Psiquiatria da Associação Brasileira de Psiquiatria (ABP)
Membro ativo de 2017 a 2019.
Vice-coordenador em 2020.

(4) Seção de Religiosidade, Espiritualidade e Psiquiatria da Associação Mundial de Psiquiatria (WPA)
Membro ativo de 2017 a 2020. Secretário eleito para Comissão Diretora para o período 2020-2023.

O GLOBO

Pesquisadores apresentam dados científicos sobre fé e saúde em evento

Congresso de Medicina e Espiritualidade acontece no Rio

Mariana Alvim

16/06/2017

RIO - Diante de remédios, hospitais, aparelhos e equipamentos de última geração, alguns especialistas têm sugerido outras palavras que devem ser incluídas nos tratamentos médicos, como gratidão, fé e empatia. Tal abordagem permeia o 11º Congresso de Medicina e Espiritualidade (Mednesp), que começou na quarta-feira e vai até amanhã no Centro de Convenções do Riocentro, no Rio. O evento deverá reunir cerca de 4 mil médicos e profissionais de saúde de várias partes do mundo.

Segundo palestrantes que participaram do primeiro dia de apresentações, o meio científico vem aos poucos acatando temáticas que relacionam espiritualidade e saúde — mesmo que esta ligação ainda seja cercada de ceticismo e preconceito. Mas eles garantem: as evidências científicas são abundantes no que diz respeito aos benefícios para a saúde de práticas como a participação em rituais religiosos, homeopatia e orações.

O cirurgião-geral Jean Rafael Santos Rodrigues destacou que há cerca de mil pesquisas na plataforma de publicações científicas PubMed com o termo "gratitude" (gratidão, em inglês). Segundo o médico, este sentimento tem caráter psicoterapêutico.

— São inúmeros os estudos que relacionam a gratidão à melhoria na saúde física e mental, na interação com o outro, no controle da dor, na socialização, na diminuição do estresse, no sistema imunológico, entre outros — apontou Rodrigues. — As metodologias também vêm diferindo um pouco, trazendo resultados distintos e um refinamento nas pesquisas.

https://oglobo.globo.com/sociedade/saude/pesquisadores-apresentam-dados-cientificos-sobre-fe-saude-em-evento-21483540

Psiquiatra Bruno Paz Mosqueiro faz estudos sobre espiritualidade e depressão Foto: Monica Imbuzeiro / Agência O Globo

RELAÇÃO COM A DEPRESSÃO

O psiquiatra Bruno Paz Mosqueiro também destacou a produção científica sobre o assunto, apresentando trabalhos já publicados em periódicos renomados. Segundo um levantamento também no PubMed, o crescimento de publicações sobre espiritualidade e saúde tem sido constante, chegando a quase 2.500 estudos divulgados em 2015 no mundo todo.

Um deles, publicado em 2014 no "JAMA Psychiatry", relaciona a espiritualidade a uma maior espessura do córtex — já se sabe que, quanto mais fina esta camada, maior a associação com a depressão. A pesquisa, da Universidade de Columbia, nos EUA, revelou também que os efeitos da espiritualidade se mostraram mais fortes nos indivíduos com maior risco de desenvolver a depressão, por histórico familiar.

— É importante abordar a espiritualidade em termos epidemiológicos, principalmente com uma base científica bem definida — afirmou Mosqueiro.

O psiquiatra vem desenvolvendo com uma equipe uma série de estudos, no Hospital de Clínicas de Porto Alegre, com pacientes com depressão. Em 2015, o grupo publicou uma pesquisa que associou a espiritualidade a uma maior resiliência e qualidade de vida, e uma menor propensão ao suicídio. Agora, os pesquisadores estão prestes a publicar um outro estudo, em que analisam o impacto da fé na neuroplasticidade cerebral.

— É interessante observar o quanto os pacientes gostam de falar da espiritualidade, mas vários estudos mostram que a maior parte das pessoas nunca foi questionada sobre sua religiosidade em consultas — destacou o psiquiatra.

12.12. Estágio na Universidade de Harvard 2018

Initiative on Health, Religion and Spirituality
https://projects.iq.harvard.edu/rshm

DANA-FARBER CANCER INSTITUTE | BRIGHAM AND WOMEN'S HOSPITAL

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April 23, 2018

Bruno Paz Mosqueiro, M.D., M.Sc. PhD Student

Porto Alegre-RS, Brazil

Dear Dr. Mosqueiro:

This is to confirm my invitation for you to visit us September 4 to October 2, 2018 at the Initiative on Health, Religion and Spirituality at Harvard University. Your visit will include discussion of the relationship between religiosity/spirituality, resilience and depression, and consideration of research in this area.

We look forward to having you join us.

Sincerely,

John R. Peteet, MD