Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pós-Graduação em Medicina: Ciências Médicas

# EFEITOS DA TERAPIA COGNITIVO-COMPORTAMENTAL NA RESPONSIVIDADE NOCICEPTIVA DE MULHERES COM FIBROMIALGIA

Autor: Rafael Mendonça da Silva Chakr

Orientador: Prof. Dr. João Carlos Tavares Brenol

Dissertação de Mestrado

2011

Universidade Federal do Rio Grande do Sul

Faculdade de Medicina

Programa de Pós-Graduação em Medicina: Ciências Médicas

# EFEITOS DA TERAPIA COGNITIVO-COMPORTAMENTAL NA RESPONSIVIDADE NOCICEPTIVA DE MULHERES COM FIBROMIALGIA

Autor: Rafael Mendonça da Silva Chakr

Orientador: Prof. Dr. João Carlos Tavares Brenol

Dissertação de Mestrado

2011

CIP - Catalogação na Publicação

Chakr, Rafael Mendonça da Silva
Efeitos da terapia cognitivo-comportamental na responsividade nociceptiva de mulheres com fibromialgia / Rafael Mendonça da Silva Chakr. -- 2011.
79 f.

Orientador: João Carlos Tavares Brenol.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Medicina: Ciências Médicas, Porto Alegre, BR-RS, 2011.

1. fibromialgia. 2. terapia cognitiva. 3. terapia comportamental. 4. medição da dor. 5. limiar da dor. I. Brenol, João Carlos Tavares, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

# Agradecimentos e dedicatórias

Este projeto de Mestrado Acadêmico foi desenvolvido na Universidade de Indiana, Indianapolis, Estados Unidos da América. Logo após o término da residência em Reumatologia no Hospital de Clínicas de Porto Alegre (HCPA), ingressei no grupo do Serviço de Reumatologia da Universidade de Indiana como professor visitante. Neste grupo, tive a oportunidade de atuar em ensino e pesquisa, com o planejamento e a execução de alguns projetos novos ou já em andamento.

O projeto de pesquisa que deu origem a esta dissertação de Mestrado Acadêmico havia sido recém-aprovado pelos órgãos reguladores locais, quando cheguei à Universidade de Indiana. Tive a oportunidade de assumir, junto com o seu investigador principal, Dr. Dennis Ang, a responsabilidade pela sua execução e conclusão. Ao longo dos quinze meses de dedicação, houve muitos ensinamentos e importante amadurecimento profissional e pessoal.

Agradeço ao Dr. Rafael Grau, professor associado de Medicina e chefe do Serviço de Reumatologia da Universidade de Indiana, por ter acreditado no meu potencial e por ter feito a permanência em Indianapolis ainda mais enriquecedora.

Agradeço ao Dr. Dennis Ang, professor assistente de Medicina da Universidade de Indiana, pela participação próxima e decisiva no meu aprimoramento profissional.

Agradeço ao Dr. Steven Mazzuca, professor e pesquisador sênior de Medicina da Universidade de Indiana, pela credibilidade depositada em mim e pelo exemplo de como um pesquisador deve ser.

Agradeço ao Dr. Kurt Kroenke, professor chanceler de Medicina da Universidade de Indiana e pesquisador do Instituto Regenstrief, pela participativa atuação no meu enriquecimento teórico na área de pesquisa clínica.

Agradeço ao Dr. Robert Tepper, professor adjunto de Medicina, da Universidade de Indiana, por ter sido o maior referencial, ao longo do tempo passado em Indianapolis.

Agradeço aos amigos Edgar Sarria-Icaza e Rita Mattiello pela amizade sincera que transcende fronteiras, e oxalá também trascenda o tempo.

Agradeço aos amigos de muitos anos Gustavo Faulhaber, Fabrizia Faulhaber, Gustavo Ayala de Sá e Ana Maria de Sá, pela importância única que têm hoje na minha vida.

Agradeço ao meu orientador, Dr. João Carlos Tavares Brenol, professor associado de Reumatologia, da Universidade Federal do Rio Grande do Sul, por seu espírito motivador, que me permitiu alcançar o meu melhor, e pela confiaça creditada no meu trabalho. De fato, sua liderança no Serviço de Reumatologia se faz presente nos seus alunos muito além do HCPA.

Agradeço ao Dr. Ricardo Machado Xavier, professor adjunto de Reumatologia da Universidade Federal do Rio Grande do Sul, pelo exemplo constante de pesquisador e pelo empenho dedicado ao aprimoramento do seu grupo, do qual tenho a honra de participar.

Agradeço ao Dr. Roberto Jorge Eichenberg, professor adjunto de Reumatologia da Universidade Federal do Rio Grande do Sul, por permitir, através de seu exemplo na feliz atuação junto à Graduação, a elaboração profissional de todo o grupo do Serviço de Reumatologia do HCPA.

Gostaria de agradecer também aos colegas de trabalho Dr. Charles Lubianca Kohem, Dr. Claiton Viegas Brenol, Dra. Sandra Machado, Dra. Iloite Scheibel, Dr. Makus Bredemeier e Dr. Odirlei André Monticielo pelos permanentes ensinamentos, que contribuem na minha construção de um profissional mais competente e humano.

Agradeço, ainda, aos então médicos residentes Dr. Pedro Schneider, Dr. Rafael Tesche, Dra. Andrese Gasparin, Dra. Daniela Viecceli, Dra. Nicole Andrade e Dra. Nizele Calegaro, pelo

contínuo incentivo na busca da melhor resposta e pela agradável convivência no Serviço de Reumatologia do HCPA.

Obrigado aos colegas de consultório Dra. Briele Keiserman e Dr. Bruno Dellaméa pela convivência diária prazerosa e inteligente, mantendo um nível de excelência profissional, apesar das adversidades do caminho.

Agradeço também às secretárias Sra. Juliana Rios e Sra. Sibeli Garcia pelo apoio incondicional às demandas em prol do benefício de todos que buscam auxílio no Serviço de Reumatologia do HCPA. Um agradecimento à parte à secretária do consultório Srta. Natália Pacheco, pela execução agradável e exemplar do seu trabalho.

Agradeço à técnica de enfermagem Sra. Lorena Koglin, que, com seu carinho e competência, torna o trabalho no ambulatório do HCPA ainda mais prazeroso e recompensatório.

Um agradecimento especial à minha amada esposa, Valentina Chakr, pela parceria maior neste projeto e em diversos outros projetos de vida.

Agradeço à minha irmã, Raquel Chakr, pela participação insubstituível na minha vida e por sempre estar ao meu lado. Agradeço à minha avó Edméa Mendonça, pela devoção incondicional à nossa família. Agradeço aos meus sogros, Valdéa e Marcos Gava, e à minha cunhada, Eveline Gava, pelo apoio e por todo o carinho de sempre.

Dedico esta dissertação a quem devo tudo e aos maiores mestres de ontem, hoje e sempre: meus pais, Tania e Jorge Chakr.

ÍNDICE GERAL

LISTA DE ABREVIATURAS

5-HTT: 5-hidroxitriptofano, serotonina

ACTH: hormônio adrenocorticotrófico

ACR: *American College of Rheumatololgy*

BASDAI: *Bath ankylosing spondylitis disease activity index*

BDNF: fator neurotrófico derivado do cérebro

COMT: catecol-O-metiltransferase

DAS-28: *disease activity score-28*

EGS: escore de gravidade de sintomas

EMG: eletromiografia

FIQ: *fibromyalgia impact questionnaire*

FM: fibromialgia

GH: hormônio do crescimento

HCPA: Hospital de Clínicas de Porto Alegre

HHA: hipotálamo-hipófise-adrenal

HLA: antígeno leucocitário humano

IASP: Associação Internacional para o Estudo da Dor

IDD: índice de dor difusa

IGF-1: fator de crescimento semelhante à insulina-1

IL-1: interleucina-1

IL-1Ra: antagonista do receptor da interleucina-1

IL-6: interleucina-6

IL-8: interleucina-8

IL-10: interleucina-10

IRB: *institutional review board*

IUPUI: *Indiana Universisty-Purdue University Indianapolis*

mA: miliampéres

ms: milissegundos

NMDA: N-metil-D-aspartato

OMERACT: *outcome measures in Rheumatology*

RNF: reflexo nociceptivo de flexão

SF-36: *medical outcomes study 36-item short-form health survey*

SNC: sistema nervoso central

TCC: terapia cognitivo-comportamental

Th-1: *T helper-1*

ÍNDICE DE FIGURAS

RESUMO

TÍTULO: Efeitos da terapia cognitivo-comportamental na responsividade nociceptiva de mulheres com fibromialgia

OBJETIVOS: Estudar os efeitos da terapia cognitivo-comportamental administrada em seis entrevistas semanais consecutivas sobre responsividade à dor na fibromialgia.

MÉTODOS: Mulheres portadoras de fibromialgia (n=32) foram randomizadas para receber terapia cognitivo-comportamental por 6 semanas ou tratamento usual. Avaliação dos desfechos foi feita no início do estudo e, também, em 6 e 12 semanas.

RESULTADOS: Nas primeiras 6 semanas, o limiar do reflexo nociceptivo aumentou no grupo que recebeu terapia cognitivo-comportamental e diminuiu no grupo recebendo tratamento usual (média ± DP, 4,4 ± 13,7mA vs. -10,2 ± 9,9mA; *P*=0,005). Esta diferença também foi demonstrada na 12ª semana (média ± DP, 7,3 ± 9,2mA para terapia cognitivo-comportamental vs. -5,4 ± 13,5mA para tratamento usual; *P*=0,01).

CONCLUSÃO: A terapia cognitivo-comportamental aumenta o limiar nociceptivo de mulheres com fibromialgia medido através do reflexo nociceptivo de flexão.

ABSTRACT

TITLE: Effects of cognitive-behavioral therapy in nociceptive responsiveness of fibromyalgia women

OBJECTIVES: To study the effects of cognitive-behavioral therapy administered in six weekly consecutive interviews on fibromyalgia pain responsiveness.

METHODS: Fibromyalgia women (n=32) were randomized to either six weeks of cognitive-behavioral therapy or usual care. Outcome measures were assessed at baseline and weeks 6 and 12 visits.

RESULTS: After six weeks of follow-up, nociceptive flexion reflex threshold was higher in cognitive-behavioral treatment group, and lower in usual care group (mean ± SD, 4,4 ± 13,7mA vs. -10,2 ± 9,9mA; *P*=0,005). This difference was also seen at week 12 (mean ± SD, 7,3 ± 9,2mA vs. -5,4 ± 13,5mA, in cognitive-behavioral therapy and usual care groups, respectively; *P*=0,01).

CONCLUSION: Cognitive-behavioral therapy increases nociceptive flexion reflex threshold among women with fibromyalgia.

# 1. INTRODUÇÃO

## 1.1. Definições

Fibromialgia (FM) é o termo utilizado para identificar pacientes com grande desconforto polissintomático crônico caracterizado por dor difusa, fadiga, alterações cognitivas, distúrbios do sono, entre outros (1).

Por ser o sintoma mais frequente, e também um dos principais domínios a serem estudados, dor é o foco deste trabalho (2, 3). Dor, segundo a Associação Internacional para o Estudo da Dor (IASP), é a experiência sensorial ou emocional associada a dano tecidual real ou potencial, ou descrita como tal (4).

De maneira didática, dor pode ser classificada em quatro tipos: nociceptiva (desencadeada por estímulos térmicos, táteis ou químicos, *e.g.* trauma), inflamatória (com inflamação tecidual ativa, *e.g.* artrite reumatóide), neuropática (lesão neurológica central ou periférica, *e.g.* neuropatia diabética) e funcional (alteração no processamento central da dor, sem lesão/inflamação tecidual), que é a dor da FM (5, 6).

Independente do tipo de dor, um estímulo, para ser considerado doloroso, precisa ultrapassar o chamado limiar nociceptivo. Assim, o limiar de dor é a intensidade mínima do estímulo percebido como doloroso (4).

A redução do limiar nociceptivo e a amplificação da resposta ao estímulo supraliminar são alterações presentes no fenômeno conhecido como sensibilização (4). Sensibilização é, portanto, o aumento na responsividade nociceptiva, seja pela facilitação na deflagração da resposta dolorosa, ou pela amplificação desta resposta.

Sensibilização pode ser dita central ou periférica, dependendo do local onde os fenômenos neurofisiológicos ocorrem. Aumento da responsividade e redução do limiar dos

nociceptores teciduais é conhecida como sensibilização periférica, ao passo que na sensibilização central ocorre o aumento da responsividade (a estímulos aferentes normais ou infraliminares) de neurônios nociceptivos no sistema nervoso central (SNC) (4). Assim, sensibilização central é a amplificação da sinalização neuronal que ocorre dentro do SNC, causando hipersensibilidade à dor (7).

Este mecanismo central da sensibilização pode ser identificado através das seguintes evidências neurofuncionais: transmissão por fibras A-beta, normalmente responsáveis pela transmissão de estímulos não-dolorosos, como toque superficial, e que pode ser determinada por estímulo elétrico ou bloqueio neuronal, disseminação de sensibilidade nociceptiva para áreas sem lesão demonstrável, sensações permanentes após cessado o estímulo, fenômeno *windup* (i.e., resposta temporal aumentada a estímulos de mesma intensidade) e manutenção da dor por estímulos de baixa frequência usualmente não-nociceptivos (7). Acredita-se que a dor na FM seja, ao menos em boa parte, causada por sensibilização central (7, 8).

Sensibilização central é identificada por suas propriedades neurofisiológicas, em que o estímulo e a resposta neuronais são medidos. Na ausência de dados neurofisiológicos, a existência de sensibilização central pode ser inferida quando há alodínia e hiperalgesia (4).

Alodínia, segundo a IASP, é dor em resposta a um estímulo não-nociceptivo (4). Este termo deve ser usado somente quando o estímulo-teste não for capaz de ativar nociceptores (e.g, ao roçar a pele suavemente). De forma mais abrangente, o aumento *latu sensu* da sensibilidade à dor é chamado de hiperalgesia. Assim, o conceito de hiperalgesia, nas novas definições da IASP, passa a abranger todas as condições de aumento de sensibilidade à dor, inclusive alodínia, que seria, então, um caso especial de hiperalgesia (4). Hiperalgesia poderia ser uma denominação clínica para o fenômeno neurofisiológico de sensibilização descrito anteriormente (4).

## 1.2. Aspectos Epidemiológicos

**Prevalência**. Estudos de diversas populações do mundo estimaram a prevalência da fibromialgia entre 0,5 e 5%, predominantemente em mulheres (3-9:1) entre a quinta e a sexta décadas de vida (5%) (9-16). Em um recente levantamento europeu, envolvendo cinco países, FM foi identificada em 14% dos pacientes atendidos em ambulatórios de reumatologia e em 4,7% da população em geral, principalmente em mulheres (2:1), entre 40 e 80 anos de idade (17). Menores níveis sócio-econômicos e educacionais parecem estar associados ao diagnóstico de FM (16).

No Brasil, estima-se uma prevalência de FM em 3,9% da população geral e em 4,4% nas pessoas de mais baixa renda, com um marcante predomínio de mulheres (39:1) entre 35 e 55 anos de idade (18, 19). Num outro estudo nacional entre idosos (média de idade de 73 ± 5,7 anos), a prevalência de FM foi de 5,5%, sendo encontrada apenas em mulheres (20).

**Fatores de risco**. Familiares de pacientes com FM têm 8,5 vezes mais chance de desenvolver a síndrome do que parentes de pacientes com artrite reumatóide (21). Aumento da frequência do haplótipo S/S do gene transportador da serotonina (5-HTT), *linkage* genético da região HLA (*human leukocyte antigen*) (*e.g.*, DR4) e polimorfismos de receptores adrenérgicos e do gene codificador da COMT (*catechol-O-methyltransferase*), enzima da via de degradação de catecolaminas, por sua vez envolvidas na regulação de opióides endógenos, já foram apontados como fatores de risco genéticos para o surgimento de FM, inclusive em trabalhos nacionais (21-24). Em outro estudo brasileiro, a presença do alelo E*2 do gene da apolipoproteína 2 mostrou ser fator de proteção da associação entre FM e estresse (25).

Trauma físico, alguns meses antes, parece estar associado ao surgimento de FM (21, 26). Num estudo transversal, FM foi 13 vezes mais frequente em quem havia apresentado

trauma cervical do que trauma em membros inferiores, estando presente, em média, 3 meses após o acidente (27).

Somatização, comportamento de busca por serviços de saúde e distúrbios do sono também estiveram associados à dor difusa crônica, como demonstrou um estudo de coorte com mais de 3.000 adultos acompanhados prospectivamente por 15 meses (28). Numa outra coorte tão grande quanto a anterior e com tempo de seguimento de 25 anos, tabagismo, alergias frequentes e hiperêmese gravídica foram descritos como preditores do surgimento de FM entre mulheres (29). Por outro lado, em uma revisão sistemática recente de estudos longitudinais, história de abuso sexual não se associou ao diagnóstico posterior de FM (30).

**Comorbidades e impacto social**. Cerca de 87% dos pacientes com FM têm pelo menos uma comorbidade e, em geral, esta população procura mais os serviços de saúde (25,1 vs. 14,8 visitas médicas anuais) do que pacientes sem FM pareados por idade e sexo, sendo considerado significativo o impacto econômico e social da síndrome (31-34).

**História Natural.** Mortalidade não parece estar aumentada na FM, embora risco de morte por suicídio, acidentes, doenças hepáticas e cerebrovasculares seja maior nestes indivíduos (35, 36). Fatores associados a suicídio em pacientes com FM são depressão, ansiedade e outras doenças psiquiátricas (36).

Ao longo da evolução da FM, dor e incapacidade funcional são duas das principais complicações (37). Fatores associados à incapacidade funcional e laboral incluem meia idade, trabalho braçal pesado prévio, dor, fadiga, fraqueza e sono não-restaurador (38).

De forma geral, há significativo comprometimento da qualidade de vida nos pacientes com FM (39), comparável ao de doenças inflamatórias incapacitantes como artrite reumatóide e espondilite anquilosante e pior do que depressão isolada (40-44). Os fatores que parecem influenciar de forma mais significativa a qualidade de vida destes pacientes são o diagnóstico

de qualquer doença psiquiátrica, a presença de repercussão da síndrome no ambiente familiar, uma percepção pior sobre o próprio estado de saúde e a história de ter consultado vários especialistas antes do diagnóstico de FM (45).

### 1.3. Fisiopatologia

**Nocicepção**. Nocicepção é o termo utilizado para se referir ao sistema de processamento da dor. Este sistema é composto, essencialmente, por duas vias neuronais antagônicas: a via pró-nociceptiva e a via antinociceptiva (46). Enquanto, pela via pró-nociceptiva, o estímulo periférico é conduzido até os centros superiores de processamento da dor, onde será interpretado na sua intensidade, duração e área anatômica envolvida, a via antinociceptiva exerce modulação permanente sobre este processamento do estímulo doloroso (Figura 1).

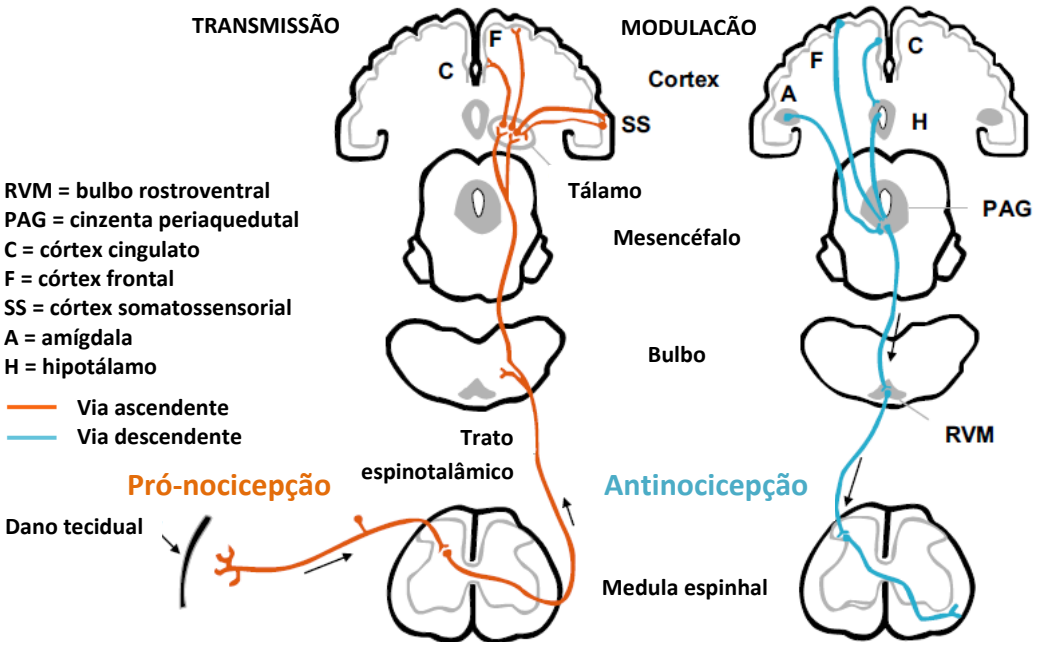


**Figura 1**: Representação esquemática das vias antinociceptivas e pró-nociceptivas. Adaptado de Russell IJ, Larson AA. *Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis*. Rheum Dis Clin North Am. 2009 May;35(2):421-35 .

Inicialmente, um sinal sensorial originado de um estímulo doloroso em tecido periférico é conduzido até o corno posterior da medula, através das fibras A-delta e C. No corno posterior da medula, ocorre a sinapse entre estes neurônios periféricos aferentes e os neurônios sensitivos medulares. Nesta sinapse, neutrotransmissores, tais como glutamato e substância P, são liberados pelo neurônio sensorial aferente, se ligando a receptores NMDA (*N-methyl-D-aspartate*) do neurônio medular. Este neurônio sensitivo medular cruza a linha mediana e ascende, pelo outro lado da medula, através do trato espinotalâmico até o tálamo, de onde é redirecionado ao córtex somatossensorial e outras regiões cerebrais. Esta é a via pró-nociceptiva, mediada, principalmente, pelo fator de crescimento neuronal, pela substância P por aminoácidos excitatórios (*e.g.*, glutamato, aspartato) e prostaglandinas (46).

Simultaneamente, sinais provenientes do córtex frontal, córtex cingulado, amígdalas e hipotálamo descendem até o corno medular posterior, onde, através de interações pré-ganglionares, isto é, na sinapse neuronal da via pró-nociceptiva, contrabalançam a magnitude do sinal pró-nociceptivo. Esta é a chamada via antinociceptiva, mediada, fundamentalmente, por serotonina, noradrenalina, dopamina e opióides endógenos (46).

Com a descoberta do fenômeno de sensibilização central, admite-se que o sistema nervoso central pode mudar, distorcer ou amplificar a dor, aumentando sua intensidade, duração e extensão espacial, numa forma que não reflete mais qualidades específicas de estímulos nocivos periféricos, mas sim estados funcionais particulares dos circuitos centrais (7). Com isso, a dor ganha uma nova dimensão: a de uma percepção ilusória. Ou seja, a sensação dolorosa, geralmente percebida a partir de estímulo nocivo, pode ser sentida, mesmo na ausência deste estímulo, o que não quer dizer que não exista, apenas que não esteja sendo originada por um evento danoso (7).

***Input* periférico**. Estímulos periféricos parecem contribuir de forma significativa no desequilíbrio nociceptivo descrito na fisiopatologia da FM, mesmo sem a identificação de lesão tecidual associada à sindrome (47, 48). *Input* nociceptivo crônico induz sensibilização central e dor amplificada, bem como ativa o eixo hipotálamo-hipófise-adrenal e o sistema simpático, participando das alterações neuroendócrinos da FM (47, 49). A ativação simpática crônica, por sua vez, sensibiliza os nociceptores periféricos, facilitando a percepção de novos estímulos e estabelecendo um ciclo vicioso (47).

Com isso, dor crônica não-funcional, (*e.g.*, nociceptiva, inflamatória, neuropática) também contribui para o desenvolvimento e para a perpetuação da dor funcional da FM. Estudos descrevendo redução do efeito analgésico de anestesia local periférica em FM reforçam esta hipótese, sugerindo a necessidade de reversão de causas não-funcionais de dor (i.e., lesão tecidual crônica) para controle da dor funcional da síndrome (50-52).

**Alterações neuro-endócrinas**. Uma série de alterações neuro-endócrinas têm sido descritas na FM, inclusive com a participação de estudos brasileiros (53-55). Grande parte destas alterações foi reportada em pesquisas que estudaram o ritmo circadiano e as respostas ao estresse, avaliando, assim, *locus coeruleus*, sistema nervoso simpático e eixo hipotálamo-hipófise-adrenal (HHA) (56, 57). Comparados a pacientes com dor não-funcional (*e.g.*, artrite reumatóide), os pacientes com FM apresentaram menor variação fisiológica diurna do cortisol plasmático (57). Além disso, quando submetidos à hipoglicemia, como forma de estresse induzido, os pacientes com FM apresentaram liberação exagerada de hormônio adrenocorticotrófico (ACTH) pela hipófise, sem elevação proporcional do cortisol (hiporresponsividade adrenal) (58). Também parece haver na FM distúrbios na produção hipofisária de hormônio do crescimento (GH, *growth hormone*), já que reduções de IGF-1

(*insulin growth factor-1*) e de GH foram mais pronunciadas nos indivíduos mais sintomáticos num estudo recente (59). Tendo em vista a influência exercida pela serotonina no funcionamento do eixo HHA, acredita-se que a deficiência deste neurotransmissor, observada nos pacientes com FM, possa explicar parte das alterações do eixo HHA notadas na síndrome (49).

Diversas alterações de neurotransmissores já foram descritas na FM. Mudanças na modulação do estímulo doloroso, tais como ativação de receptores NMDA (*N-methyl-D-aspartate*), presentes no corno posterior da medula, e elevação de níveis séricos de BDNF (*brain-derived neurotrophic factor*) foram relatadas (60, 61). Níveis liquóricos de substância P, importante neurotransmissor pró-nociceptivo, estão aumentados em pacientes com FM (62). Níveis aumentados de metabólitos dos aminoácidos excitatórios glutamato e aspartato também estão correlacionados a mais dor em pacientes com FM (63). Além destas modificações pró-nociceptivas, também já foram observadas alterações da via antinociceptiva, tais como redução dos metabólitos de serotonina e noradrenalina, importantes neurotransmissores inibitórios (64-66). Com isso, hiperexcitação pró-nociceptiva e inibição antinociceptiva compõem o conjunto neuroquímico funcional da FM.

Disfunção simpática (hiperatividade e hiporreatividade) pode explicar parte dos sintomas da FM, tais como ansiedade, ressecamento mucocutâneo, fenômeno de Raynaud e irritabilidade intestinal (67). FM poderia ser conceituada como uma tentativa fracassada do sistema nervoso autônomo se adaptar a um ambiente hostil (68).

Apesar de hipovitaminose D ser causa conhecida de dor difusa crônica, podendo, assim, mimetizar os sintomas de FM, não há, até o momento, evidências consistentes o suficiente para se afirmar que baixos níveis de vitamina D estejam associados à síndrome (69, 70).

**Alterações imunológicas e inflamatórias**. Vários estudos destacam o papel da autimunidade na fisiopatologia da FM, embora ainda não haja conhecimento bem estabelecido nesta área. Apesar da concomitância de outras doenças autoimunes (*e.g.*, lúpus eritematoso sistêmico, síndrome de Sjögren e tireoidites) e da presença de autoanticorpos em até 30% dos pacientes com FM, ainda não há resultados bem estabelecidos que apontem para uma associação entre mecanismos autoimunes específicos e o desenvolvimento da síndrome (49, 71-73). Dentre as citocinas avaliadas, elevações de IL-8 (interleucina-8), IL-6, IL-10 e IL-1 Ra já foram descritas, mas nem sempre reproduzidas (74, 75). Algumas destas citocinas (*e.g.*, IL-1 e IL-6) são capazes de ativar o eixo HHA e poderiam estar relacionadas às alterações neuroendócrinas de resposta ao estresse observadas na FM. Além disso, o início dos sintomas da síndrome associa-se a estresse emocional, que pode afetar a produção de citocinas pró-inflamatórias e a resposta tipo Th-1.(49)

Em estudo piloto, estresse oxidativo celular e disfunção mitocondrial estiveram associados à FM *versus* controles saudáveis (76). Estes resultados preliminares apontam a disfunção oxirredutiva celular como possível mecanismo fisiopatológico a ser estudado na FM.

## 1.4. Manifestações clínicas

O principal sintoma da FM é dor difusa crônica, geralmente caracterizada por alodínia ou hiperalgesia em áreas articulares e, principalmente, não-articulares, presentes por mais de 3 meses. Além de dor difusa crônica, fadiga, distúrbios do sono, rigidez, limitação funcional, alterações cognitivas (*e.g.*, memória, atenção) e humor deprimido fazem parte do espectro clínico da FM (3, 77-79). Depressão, ansiedade, síndrome do intestino irritável, enxaqueca, distúrbios temporomandibulares e disfunção sexual também são comorbidades frequentes nos pacientes com FM (77, 80).

Do ponto de vista afetivo, FM é uma condição debilitante, associando-se a uma ativação defensiva aumentada contra estímulos potencialmente nocivos (81). Além disso, pacientes com FM acham que têm menos saúde do que pessoas com artrite reumatóide, principalmente saúde mental (82). Dor e fadiga parecem ser os sintomas que mais incomodam os pacientes com FM (83). De forma semelhante ao que ocorre em outros países, no Brasil, pacientes com FM parecem ter mais dor, incapacidade profissional, fadiga, cansaço matinal, rigidez, ansiedade e depressão do que pessoas sem dor ou com dor regional (19, 84).

Comparados a indivíduos sem FM, os pacientes com FM apresentam mais sinais e sintomas neurológicos, tais como alterações de pares cranianos (*e.g.*, IX e X), disfunções sensoriais (*e.g.*, parestesias, fotofobia), motoras (*e.g.*, fraqueza) e de marcha (*e.g.*, desequilíbrio) (85). Apesar da sua natureza funcional (i.e., sem lesão tecidual), a dor na FM tem muitas vezes características neuropáticas, como por exemplo hiperalgesia profunda, parestesia, dor em ardência ou agulhada (86). Especula-se que estas características poderiam estar relacionadas às alterações neurofisiopatológicas da síndrome, como sensiblização central e disfunção autonômica (68, 86, 87).

A FM pode interferir em medidas de avaliação de atividade de doenças inflamatórias, como artrite reumatóide e espondilite anquilosante, especialmente através dos componentes subjetivos de índices como o DAS-28 (*disease activity score-28*) e o BASDAI (*Bath ankylosing spondylitis disease activity index*) (88-90). Acredita-se que pacientes com doenças inflamatórias e FM possam apresentar índices falsamente elevados de atividade de doença, o que pode interferir na decisão terapêutica durante o seu acompanhamento.

Os pacientes com FM são um grupo heterogêneo de indivíduos que apresentam manifestações clínicas diversas. Tentativas recentes de alocação dos pacientes com FM em subgrupos têm sido feitas, a partir de características clínicas e fisiopatológicas em comum, com

o intuito de, em última análise, identificar indivíduos com melhor resposta terapêutica a determinada opção de tratamento (87, 91).

Em estudo transversal realizado na Alemanha, os mais de 3.000 participantes foram classificados em cinco subgrupos, de acordo com predominância de certos sintomas neurossensoriais (i.e., dor em ardência, dor em agulhada, alodínia, crises de dor, dor por estímulos térmicos, anestesia e dor por estímulos pressóricos) e comorbidades (i.e., depressão, ansiedade e distúrbios do sono): (1) dor por estímulos térmicos (17%); (2) dor em agulhada (21%); (3) dor por estímulos pressóricos e alodínia (20%); (4) dor por estímulos pressóricos e crises de dor (17%); (5) depressão e distúrbios do sono, sem diferenças entre as características de dor (25%) (87).

Em outro estudo, os pacientes com FM foram distribuídos em quatro subgrupos, conforme a predominância de sintomas físicos e cognitivos/psicológicos: (1) sintomas físicos e cognitivos/psicológicos intensos; (2) sintomas físicos moderados e cognitivos/psicológicos intensos; (3) sintomas físicos moderados e cognitivos/psicológicos baixos; (4) sintomas físicos e cognitivos/psicológicos baixos (91). O subgrupo mais sintomático apresentou maiores taxas de utilização dos serviços de saúde e maior dificuldade em lidar com seus sintomas (91).

### 1.5. Avaliação por biomarcadores

Um dos principais focos de pesquisa em FM é a busca de biomarcadores acurados para seu diagnóstico e rastreamento, bem como de medidas objetivas de avaliação de atividade de doença, que possam balizar a prática clínica e representar desfechos clínicos em estudos (92). Uma lista de domínios a serem pesquisados foi definida pelo grupo de estudos de medidas de desfecho em Reumatologia (OMERACT), incluindo dor, fadiga, avaliação global da saúde pelo paciente e capacidade funcional multidimensional (93).

Numa revisão sistemática, considerando-se marcadores genéticos, medidas de dor experimental, sono e atividade, sistemas de resposta ao estresse e hormônios sexuais, alterações musculares, bioquímicas e sorológicas, apenas os testes com dor experimental correlacionaram-se a desfechos clínicos em estudos longitudinais (92). Estes testes de avaliação experimental de dor incluem contagem de pontos dolorosos, limiares de dor por pressão, estímulos térmicos e elétricos, diminuição do controle inibitório nocivo difuso, imagens neurofuncionais e potenciais relacionados a eventos (92). Destes, o reflexo nociceptivo de flexão (RNF), detectado a partir de retirada de membro inferior após estimulação elétrica do nervo sural, parece ser o mais fidedigno, com boa correlação com domínios clínicos (*e.g.*, dor) e sem significativa variabilidade interindividual (94-96).

Quando fibras fibras A-delta de um membro são estimuladas, um impulso nociceptivo é transmitido à medula, disparando um reflexo protetor de retirada no membro ipsilateral. Este reflexo nociceptivo de flexão (RNF) é polissináptico e sua função maior é a proteção tecidual de evento nocivo, diminuindo o dano potencial associado (97).

Estudos prévios evidenciaram que a intensidade do estímulo que deflagra o RNF (limiar do RNF) se correlaciona de maneira significante com o limiar subjetivo de dor, e a magnitude do RNF se correlaciona com a intensidade de dor (97). Assim, o RNF pode ser empregado experimentalmente de duas formas: o limiar do RNF pode ser utilizado como medida objetiva do limiar nociceptivo e a magnitude do RNF pode ser utilizada para avaliar mudanças na resposta nociceptiva a estímulos supraliminares constantes (97).

A presença e a magnitude do RNF são avaliadas diretamente por eletromiografia (EMG) do músculo bíceps femoral (Figura 2). No entanto, a leitura eletromiográfica do bíceps femoral após estímulo elétrico não é unicamente influenciada pela ativação das fibras A-delta. O estímulo elétrico ativa também fibras A-beta que pode deflagrar contração precoce (em até 70

ms) do bíceps femoral (reflexo RII) (97). Além disso, contrações musculares tardias (após 150 ms) podem estar associadas a movimentos voluntários (97). Para evitar contaminação com estas respostas não-nociceptivas, o RNF (um componente do reflexo RIII) deve ser pesquisado no intervalo entre 90 e 150 ms após a deflagração do estímulo elétrico (97).

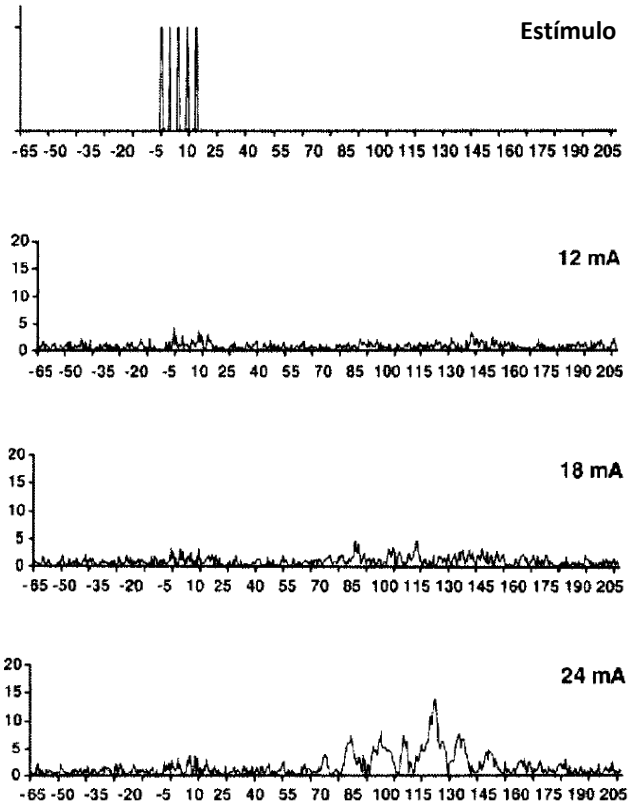


**Figura 2**: Leitura eletromiográfica de um indivíduo submetido a estímulos elétricos de diferentes intensidades. Adaptado de Rhudy JL *et al*. *Taxometric analysis of biceps femoris EMG following electrocutaneous stimulation over the sural nerve: Determining the latent structure of the nociceptive flexion reflex (NFR).* Int J Psychophysiol. 2008 Jul;69(1):18-26.

A detecção do RNF não parece ser influenciada por catastrofização, hipertensão arterial, nem pelo ciclo menstrual, mas sim por medicamentos de ação central, analgésicos, raça, sexo, antecipação e sentimentos (afeto) (98-108). Padronização do método de execução e interpretação do exame para detecção do RNF foi estabelecida, para otimizar sua acurácia (96, 109, 110).

Os poucos estudos desenvolvidos em FM utilizando o RNF como medida objetiva de responsividade à dor e de sensibilização central obtiveram resultados promissores do método (8, 111). Num estudo transversal com 125 participantes (85 com FM e 40 controles saudáveis pareados por idade e sexo), Desmeules *et al*. demonstraram uma redução da ordem de 33% no limiar nociceptivo dos indivíduos com FM detectado a partir do RNF, sendo estimado em 27,6 mA o ponto de corte que permitiria, com sensibilidade de 73% e especificidade de 80%, identificar o déficit antinociceptivo nestes pacientes. Uma redução no limiar nociceptivo medido pelo RNF de magnitude semelhante foi reproduzida por Banic *et al*., ao comparar indivíduos com FM versus controles saudáveis. Até o momento, a importância clínica das variações quantificadas do limiar nociceptivo em FM ainda não foram bem definidas.

A excitabilidade neuronal da medula, por sua vez, pode ser estudada através do fenômeno de *windup*, que é a resposta temporal aumentada a estímulos de mesma intensidade aplicados numa frequência determinada (112). Pacientes com FM apresentam *windup* e lentidão na resolução da dor, diferentemente daqueles sem FM (113-115).

Estudos de neuroimagem demonstraram que dor na FM associa-se a ativação de diversas redes de conectividade cerebrais, bem como alterações neuroquímicas (*e.g.*, ligação a receptores opióides) e neuroanatômicas (*e.g.*, atrofia cortical) (116, 117). As evidências de alterações neurofuncionais também se deram nos estudos de avaliação eletroencefalográfica,

em que pacientes com FM apresentaram mais anormalidades do que indíviduos saudáveis (118).

Um dos principais aspectos da síndrome é o seu impacto na qualidade de vida. Dois questionários de avaliação de qualidade de vida se destacaram em estudo brasileiro realizado por Assumpção *et al.*: o *fibromyalgia impact questionnaire* (FIQ), que apresentou a melhor acurácia, e o *medical outcomes study 36-item short-form health survey* (SF-36) (119).

## 1.6. Diagnóstico

Em 1990, com o intuito de uniformizar o emprego científico do termo fibromialgia, foram publicados pelo Colégio Americano de Reumatologia (*American College of Rheumatology, ACR*) os critérios de classificação da síndrome (Anexo I) (120). Recentemente, objetivando aumentar a acurácia diagnóstica, foram divulgados critérios de diagnóstico e escala de gravidade de sintomas da FM (3). Com estes novos critérios, queixas como fadiga, distúrbios cognitivos e outros sintomas somáticos passaram a ser considerados (121). A necessidade de avaliar evolutivamente os pacientes com FM através de escala de gravidade de sintomas também foi contemplada nos novos critérios diagnósticos (121). A título de facilitar a execução de estudos epidemiológicos e clínicos, os critérios de diagnóstico de FM e a escala de gravidade de sintomas foram posteriormente modificados (Anexo II) (121).

## 1.7. Tratamento

Como nas doenças crônicas em geral, o tratamento da FM busca amenizar sintomas, desacelerar a progressão da doença, estimular o envolvimento do paciente no seu autocuidado, aprimorar capacidade funcional e restaurar a dignidade do indivíduo (2).

O avanço do conhecimento sobre a fisiopatologia da FM tem permitido o uso de medicações mais apropriadas e tem incorporado técnicas não-farmacológicas mais eficazes ao arsenal terapêutico do médico nos seus diversos níveis de atuação (122, 123).

Além disso, os aspectos populacionais da FM também devem ser mais bem conhecidos, como identificado em levantamento realizado por Moretti *et al*. no Brasil, para que políticas mais eficazes possam ser implementadas (124).

**Abordagens terapêuticas**. As recomendações de tratamento da FM destacam exercício aeróbico, terapia cognitivo-comportamental (TCC), amitriptilina e tratamento combinado (medidas farmacológicas e não-farmacológicas) como as principais opções terapêuticas a serem aplicadas (125).

A coexistência de síndromes dolorosas regionais dificulta o manejo da FM, provavelmente por perpetuar o fenômeno de sensibilização central através do *input* periférico. Assim, causas periféricas de dor localizada (*e.g.*, contratura, tendinite, bursite, artrite) devem ser sistematicamente investigadas e tratadas no acompanhamento dos pacientes com FM (52).

**Tratamento farmacológico**. O tratamento farmacológico da FM inclui várias classes de medicamentos (*e.g.*, analgésicos simples, analgésicos opióides, relaxantes musculares, antidepressivos, anticonvulsivantes, agonistas dopaminérgicos), mas nenhuma destas drogas atua de forma completa na síndrome, melhorando apenas um número limitado de sintomas (126). Por isso, a abordagem combinada, incluindo medidas farmacológicas e não-farmacológicas, deve ser usada desde o início (126).

Em uma metanálise comparando pregabalina, duloxetina, amitriptilina ou nortriptilina, fluoxetina, milnacipram, gabapentina, pramipexol e paracetamol com tramadol, não houve superioridade de um medicamento sobre os demais, sendo todos superiores ao placebo (127).

Em outra análise comparativa, duloxetina e pregabalina foram superiores a milnacipram na redução de dor e distúrbios do sono, duloxetina foi superior a milnacipram e pregabalina na redução de humor deprimido e milnacipram e pregabalina foram superiores a duloxetina na redução de fadiga (128). Além disso, o risco de cefaléia e náusea foi maior com duloxetina e milnacipram, e o risco de diarréia foi maior com duloxetina (128).

O uso de antidepressivos está associado a melhora de dor, fadiga, distúrbios do sono, depressão e qualidade de vida nos pacientes com FM (129).

Pregabalina, da classe dos anticonvulsivantes, parece ser eficaz no tratamento de FM, melhorando, principalmente, a dor e os distúrbios do sono (130).

O uso combinado de lidocaína por via endovenosa e amitriptilina por via oral não foi eficaz no tratamento da dor em pacientes com FM, como demonstrado em estudo brasileiro por Vlainich *et al*. (131).

**Tratamento não-farmacológico**. A intervenção psicológica em FM parece melhorar dor, sono, depressão, catastrofização e estado funcional, de forma semelhante ao benefício observado em estudos de outras condições dolorosas e de tratamento farmacológico na FM (132). Em análises comparativas, TCC foi superior às outras intervenções psicológicas no controle da dor em FM (132).

Abordando especificamente terapia cognitivo-comportamental (TCC), uma revisão sistemática com revisão crítica de ensaios clínicos randomizados estudou a sua eficácia na FM, e constatou o efeito benéfico desta intervenção na capacidade de o indivíduo em lidar com a dor, no humor deprimido e no comportamento de busca por cuidados em saúde (133). Dor é o principal domínio que os pacientes com FM gostariam de ter resolvido (83).

Como o próprio nome sugere, terapia cognitivo-comportamental é composta por duas frentes de atuação: uma abordagem cognitiva e outra comportamental. A terapia cognitiva está baseada na premissa de que a modificação de pensamentos perturbadores gera mudanças nos sentimentos (afeto) e no comportamento (134). Assim, os chamados “desvios do pensamento”, tais como supergeneralização, amplificação de aspectos negativos, minimização de aspectos positivos e catastrofização são confrontados e substituídos por pensamentos mais realísticos e efetivos, reduzindo, assim, perturbações emocionais e comportamento autodestrutivo (135). Na FM, catastrofização, isto é, o pensamento de que o pior desfecho possível vá acontecer, está associada a intensidade de dor, limitação funcional e perturbações afetivas (136-138).

De forma complementar, a terapia comportamental enfatiza o uso de técnicas de mudança comportamental para fazer prevalecer o comportamento adequado. Com uma abordagem mais prática e menos focada no pensamento, a terapia comportamental pretende modular as atitudes frente às questões do dia-a-dia através de reforço positivo e negativo das decisões tomadas (135). Na FM, várias técnicas comportamentais são aplicáveis, incluindo ativação comportamental (retomar atividades cotidianas descontinuadas), exercícios gradativos, regularidade de atividades (dosando atividades nos melhores e piores momentos da síndrome), redução de comportamentos associados a ganho secundário, higiene do sono e técnicas de relaxamento (*e.g.*, respiração, imagens, relaxamento muscular progressivo) (135).

A TCC tem se mostrado eficaz no tratamento de depressão e ansiedade, condições frequentemente associadas à FM (139-141). Além disso, TCC também se mostrou eficaz no tratamento de condições de dor crônica (142). Considerando-se o fato de que TCC não seja uma intervenção isolada, existe evidência suficiente de que TCC possa ser um tratamento adjuvante efetivo para alguns pacientes com FM, melhorando, inclusive, dor (135, 143-147).

Os melhores resultados da TCC, bem como de outras medidas não-farmacológicas, têm-se obtido no início dos sintomas, especialmente naqueles pacientes com um componente mais importante de perturbação emocional (148).

Associado à TCC, o exercício regular é uma medida a ser recomendada (123). Programa de exercícios combinados (aeróbico, reforço muscular e alongamento) parece trazer benefícios adicionais aos pacientes com FM, em relação ao programa de exercício aeróbico isolado (149). Além disso, exercícios como caminhadas também apresentam melhora em vários sintomas da síndrome, como demonstrado por Kayo *et al*. em ensaio brasileiro (150). Em outro estudo brasileiro, Assumpção *et al*. identificaram força muscular, flexibilidade e equilíbrio como os principais fatores associados à dor em pacientes com FM (151). Quanto a exercícios na água, hidroterapia parece melhorar dor e qualidade de vida a curto prazo (152).

O aumento das atividades cotidianas por si só (*e.g*., caminhadas, tarefas domésticas) parece ter efeito benéfico em FM, semelhante a programas de exercício regular (153, 154). Dentre todos os pacientes com FM, aqueles que são mais ativos fisicamente parecem ser os que apresentam melhor qualidade de vida, demonstrando a interrelação entre aspectos emocionais e físicos da síndrome (155).

Apesar de diversas evidências em favor das medidas não-farmacológicas no tratamento da FM, os resultados positivos observados não parecem se sustentar por mais de 6 meses, mostrando a necessidade de estratégias de longo prazo mais efetivas (156).

Não existem evidências científicas de que as terapias complementares e alternativas sejam, de fato, eficazes no tratamento da FM (157). Outras técnicas, tais como a estimulação transcraniana por corrente direta, têm sido estudadas em nosso país com resultados promissores no controle da dor (158).

**Tratamento combinado**. Segundo o Consenso Brasileiro de Tratamento da Fibromialgia, a estratégia ideal exige uma abordagem multidisciplinar com a combinação de tratamento farmacológico e não-farmacológico, devendo a proposta terapêutica ser discutida com o paciente (159).

O tratamento com intervenções farmacológicas e não-farmacológicas (tratamento combinado) melhora, a curto prazo, a dor, a fadiga, os sintomas depressivos, a qualidade de vida e o condicionamento físico, sendo o benefício para este último mantido por alguns meses (160).

## 1.8. Prognóstico

A FM não altera a expectativa de vida dos pacientes (35, 36), no entanto incapacidade funcional e aposentadoria precoce parecem estar associadas a esta condição em até 25% dos casos (161). Dor, catastrofização e depressão são características mais comumente associadas à falha terapêutica (162).

Por outro lado, a melhora significativa dos níveis de dor parece predizer boa resposta terapêutica por mais tempo, inclusive em outros domínios, como qualidade de vida (163).

Atualmente, têm-se buscado marcadores de resposta às diferentes opções terapêuticas disponíveis, já que a individualização do tratamento parece otimizar o seu sucesso (87, 163, 164).

## 1.9. Perspectivas de pesquisa

Alguns pontos sugeridos para pesquisas futuras em FM são:

- Melhorar o conhecimento das diferentes funções desempenhadas pelos diferentes fatores neuroendocrinoimunológicos na etiopatogenia da FM (49).

- Dor, fadiga, dolorimento, avaliação global pelo paciente, capacidade funcional e distúrbios do sono são considerados os domínios mais importantes para futuros ensaios clínicos (93).

- Individualização do tratamento pela categorização dos pacientes em grupos de apresentação clínica merece ser mais bem estudada como estratégia na busca de melhores respostas (87, 91).

- Melhorar os métodos de avaliação dos pacientes com FM, através de definições consensuais sobre mudanças clinicamente significativas nos domínios estudados e do desenvolvimento de instrumentos de medida altamente qualificados (2).

- Identificação de biomarcadores acurados para o diagnóstico e acompanhamento dos pacientes com FM (92, 93).

Como parte do seguimento desta linha de pesquisa, pretendemos implementar o Ambulatório de Fibromialgia do Serviço de Reumatologia do Hospital de Clínicas de Porto Alegre, com o objetivo de atender às crescentes demandas por melhor conhecimento científico desta condição e oferecer assistência de qualidade à população.

Atualmente, a busca por biomarcadores efetivos no diagnóstico e acompanhamento dos pacientes com FM deve ser uma estratégia inicial de pesquisa clínica a ser implementada neste ambulatório, aproveitando também o conhecimento adquirido com a execução deste projeto.

## 2. REVISÃO DA LITERATURA

Como parte da fundamentação teórica deste projeto, vários trabalhos estudando a associação entre dor e manifestações afetivas/neurofuncionais (*e.g.*, disfunção cognitiva, depressão) foram analisados. O mecanismo fisiopatológico principal destes estudos foi a sensibilização central.

Devido à sua natureza objetiva e comprovada acurácia, foi utilizado neste projeto o reflexo nociceptivo de flexão (RNF), para avaliar o fenômeno de sensibilização central (97, 109, 110).

A seguir, alguns dos principais estudos correlatos.

**Fibromialgia e depressão**. Pacientes com FM e depressão têm maior *deficit* antinociceptivo e mais dor clínica do que aqueles com FM sem depressão (164). FM e depressão apresentam alterações fisiopatológicas em comum (165, 166), tais como mudanças quantitativas e funcionais de neurotransmissores (167, 168) e mecanismos de hiperexcitabilidade neuronal semelhantes à sensibilização central (169).

**Fibromialgia e disfunção cognitiva**. Disfunção cognitiva associada à FM não pode ser atribuída exclusivamente às condições psiquiátricas concomitantes (170). Existe uma relação da disfunção cognitiva com o nível de dor, sugerindo uma ponte entre aspectos orgânicos (i.e., neuroquímicos) e emocionais nesta situação (170). Em FM, melhora na dor está associada a melhora em outros aspectos, tais como fadiga, capacidade funcional, depressão e qualidade de vida (163).

**Tratamento não-farmacológico da fibromialgia**. As terapias não-farmacológicas deveriam ser utilizadas com mais frequência nas condições de dor crônica, devido ao efeito geralmente modesto e parcial das medicações empregadas (171). Orientação, TCC e

exercícios têm benefícios expressivos em FM, mas na prática clínica raramente são utilizados (171).

A terapia cognitivo-comportamental na FM visa melhorar humor, estresse, convívio com a dor e capacidade de resolução de problemas, através da modificação de pensamentos perturbadores e de intervenções corporais, tais como higiene do sono, treinamento em relaxamento e regularidade de atividades diárias. Na FM, o objetivo principal da TCC é aumentar o automanejo, que inclui induzir os pacientes a acreditar na sua capacidade de lidar com a dor e outros sintomas, bem como a tomar providências para melhorá-los, otimizando, assim, sua capacidade funcional (135). Atualmente, a adição de TCC ao tratamento medicamentoso usual apresenta resultados promissores, mas que necessitariam de replicação em outros estudos, como ensaios clínicos randomizados (135).

Visando avaliar de forma objetiva os efeitos de intervenções não-farmacológicas nos sintomas da FM, vários estudos foram publicados (135). No entanto, apenas um ensaio com técnicas de relaxamento muscular progressivo buscou correlações entre tratamento não-farmacológico e RNF (172). Não foram encontrados estudos publicados que tenham analisado os efeitos da TCC na responsividade à dor medida de forma objetiva pelo RNF.

## 3. OBJETIVOS

### GERAL

Estudar os efeitos da terapia cognitivo-comportamental administrada em seis entrevistas semanais consecutivas sobre a responsividade à dor de mulheres portadoras de fibromialgia após doze semanas de acompanhamento, através da mudança no limiar nociceptivo medido pelo reflexo nociceptivo de flexão.

### ESPECÍFICOS

(1) Estudar os efeitos da terapia cognitivo-comportamental na dor e no impacto causado pela fibromialgia.

(2) Estudar a capacidade de o limiar nociceptivo medido pelo reflexo nociceptivo de flexão identificar resposta terapêutica evolutiva em mulheres com fibromialgia.

## 4. REFERÊNCIAS BIBLIOGRÁFICAS


1. Wolfe F. Fibromyalgianess. Arthritis Care & Research. 2009;61(6):715-858.
2. Williams DA, Schilling S. Advances in the assessment of fibromyalgia. Rheum Dis Clin North Am. 2009 May;35(2):339-57.
3. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010 May;62(5):600-10.
4. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain. 2008 Jul 31;137(3):473-7.
5. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004 Mar 16;140(6):441-51.
6. Heymann RE, Provenza JR. Os mecanismos de dor nas doenças reumáticas. In: Heymann RE, editor. Dores musculoesqueléticas localizadas e difusas. São Paulo: Planmark Editora; 2010.
7. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. Pain. 2010 Oct 18;Epub on line.
8. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum. 2003 May;48(5):1420-9.
9. White KP, Harth M. Classification, epidemiology, and natural history of fibromyalgia. Curr Pain Headache Rep. 2001 Aug;5(4):320-9.
10. Yunus MB. The role of gender in fibromyalgia syndrome. Curr Rheumatol Rep. 2001 Apr;3(2):128-34.
11. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis. 2001 Nov;60(11):1040-5.
12. Haq SA, Darmawan J, Islam MN, Uddin MZ, Das BB, Rahman F, et al. Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study. J Rheumatol. 2005 Feb;32(2):348-53.
13. Wolfe F, Cathey MA. Prevalence of primary and secondary fibrositis. J Rheumatol. 1983 Dec;10(6):965-8.
14. Cardiel MH, Rojas-Serrano J. Community based study to estimate prevalence, burden of illness and help seeking behavior in rheumatic diseases in Mexico City. A COPCORD study. Clin Exp Rheumatol. 2002 Sep-Oct;20(5):617-24.
15. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995 Jan;38(1):19-28.
16. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol. 1999 Jul;26(7):1570-6.
17. Branco JC, Bannwarth B, Failde I, Abello Carbonell J, Blotman F, Spaeth M, et al. Prevalence of fibromyalgia: a survey in five European countries. Semin Arthritis Rheum. 2009 Jun;39(6):448-53.
18. Senna ER, De Barros AL, Silva EO, Costa IF, Pereira LV, Ciconelli RM, et al. Prevalence of rheumatic diseases in Brazil: a study using the COPCORD approach. J Rheumatol. 2004 Mar;31(3):594-7.
19. Assumpcao A, Cavalcante AB, Capela CE, Sauer JF, Chalot SD, Pereira CA, et al. Prevalence of fibromyalgia in a low socioeconomic status population. BMC Musculoskelet Disord. 2009;10:64.
20. Santos AM, Burti JS, Lopes JB, Scazufca M, Marques AP, Pereira RM. Prevalence of fibromyalgia and chronic widespread pain in community-dwelling elderly subjects living in Sao Paulo, Brazil. Maturitas. 2010 Nov;67(3):251-5.

21. Oliver JE, Silman AJ. What epidemiology has told us about risk factors and aetiopathogenesis in rheumatic diseases. Arthritis Res Ther. 2009;11(3):223.
22. Vargas-Alarcon G, Fragoso JM, Cruz-Robles D, Vargas A, Martinez A, Lao-Villadoniga JI, et al. Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains. Arthritis Rheum. 2009 Jul;60(7):2169-73.
23. Matsuda JB, Barbosa FR, Morel LJ, Franca Sde C, Zingaretti SM, da Silva LM, et al. Serotonin receptor (5-HT 2A) and catechol-O-methyltransferase (COMT) gene polymorphisms: triggers of fibromyalgia? Rev Bras Reumatol. 2010 Apr;50(2):141-9.
24. Carvalho LS, Correa H, Silva GC, Campos FS, Baiao FR, Ribeiro LS, et al. May genetic factors in fibromyalgia help to identify patients with differentially altered frequencies of immune cells? Clin Exp Immunol. 2008 Dec;154(3):346-52.
25. Becker RM, da Silva VK, Machado Fda S, dos Santos AF, Meireles DC, Mergener M, et al. Association between environmental quality, stress and APOE gene variation in fibromyalgia susceptibility determination. Rev Bras Reumatol. 2010 Dec;50(6):617-24.
26. Al-Allaf AW, Dunbar KL, Hallum NS, Nosratzadeh B, Templeton KD, Pullar T. A case-control study examining the role of physical trauma in the onset of fibromyalgia syndrome. Rheumatology (Oxford). 2002 Apr;41(4):450-3.
27. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. Arthritis Rheum. 1997 Mar;40(3):446-52.
28. Gupta A, Silman AJ, Ray D, Morriss R, Dickens C, MacFarlane GJ, et al. The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study. Rheumatology (Oxford). 2007 Apr;46(4):666-71.
29. Choi CJ, Knutsen R, Oda K, Fraser GE, Knutsen SF. The association between incident self-reported fibromyalgia and nonpsychiatric factors: 25-years follow-up of the Adventist Health Study. J Pain. 2010 Oct;11(10):994-1003.
30. Paras ML, Murad MH, Chen LP, Goranson EN, Sattler AL, Colbenson KM, et al. Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. JAMA. 2009 Aug 5;302(5):550-61.
31. Lachaine J, Beauchemin C, Landry PA. Clinical and economic characteristics of patients with fibromyalgia syndrome. Clin J Pain. 2010 May;26(4):284-90.
32. Thompson JM, Luedtke CA, Oh TH, Shah ND, Long KH, King S, et al. Direct medical costs in patients with fibromyalgia: Cost of illness and impact of a brief multidisciplinary treatment program. Am J Phys Med Rehabil. 2010 Jan;90(1):40-6.
33. Robinson RL, Birnbaum HG, Morley MA, Sisitsky T, Greenberg PE, Claxton AJ. Economic cost and epidemiological characteristics of patients with fibromyalgia claims. J Rheumatol. 2003 Jun;30(6):1318-25.
34. Boonen A, van den Heuvel R, van Tubergen A, Goossens M, Severens JL, van der Heijde D, et al. Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis. Ann Rheum Dis. 2005 Mar;64(3):396-402.
35. Wolfe F, Hassett AL, Walitt B, Michaud K. Mortality in fibromyalgia: a study of 8,186 patients over thirty-five years. Arthritis Care Res (Hoboken). 2010 Jan;63(1):94-101.
36. Dreyer L, Kendall S, Danneskiold-Samsoe B, Bartels EM, Bliddal H. Mortality in a cohort of Danish patients with fibromyalgia: increased frequency of suicide. Arthritis Rheum. 2010 Oct;62(10):3101-8.
37. Hawley DJ, Wolfe F. Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. J Rheumatol. 1991 Oct;18(10):1552-7.

38. White KP, Speechley M, Harth M, Ostbye T. Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: the London Fibromyalgia Epidemiology Study. Arthritis Rheum. 1999 Jan;42(1):76-83.
39. Marques AP, Ferreira EA, Matsutani LA, Pereira CA, Assumpcao A. Quantifying pain threshold and quality of life of fibromyalgia patients. Clin Rheumatol. 2005 Jun;24(3):266-71.
40. Martinez JE, Ferraz MB, Sato EI, Atra E. Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. J Rheumatol. 1995 Feb;22(2):270-4.
41. Strombeck B, Ekdahl C, Manthorpe R, Wikstrom I, Jacobsson L. Health-related quality of life in primary Sjogren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol. 2000;29(1):20-8.
42. Ovayolu N, Ovayolu O, Karadag G. Health-related quality of life in ankylosing spondylitis, fibromyalgia syndrome, and rheumatoid arthritis: a comparison with a selected sample of healthy individuals. Clin Rheumatol. 2011 May;30(5):655-64.
43. Yoshikawa GT, Heymann RE, Helfenstein M, Jr., Pollak DF. A comparison of quality of life, demographic and clinical characteristics of Brazilian men with fibromyalgia syndrome with male patients with depression. Rheumatol Int. 2010 Feb;30(4):473-8.
44. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health Qual Life Outcomes. 2008;6:8.
45. Ubago Linares Mdel C, Ruiz-Perez I, Bermejo Perez MJ, Olry de Labry-Lima A, Hernandez-Torres E, Plazaola-Castano J. Analysis of the impact of fibromyalgia on quality of life: associated factors. Clin Rheumatol. 2008 May;27(5):613-9.
46. Russell IJ, Larson AA. Neurophysiopathogenesis of fibromyalgia syndrome: a unified hypothesis. Rheum Dis Clin North Am. 2009 May;35(2):421-35.
47. Vierck CJ, Jr. Mechanisms underlying development of spatially distributed chronic pain (fibromyalgia). Pain. 2006 Oct;124(3):242-63.
48. Staud R. Is it all central sensitization? Role of peripheral tissue nociception in chronic musculoskeletal pain. Curr Rheumatol Rep. 2010 Dec;12(6):448-54.
49. Di Franco M, Iannuccelli C, Valesini G. Neuroendocrine immunology of fibromyalgia. Ann N Y Acad Sci. 2010 Apr;1193:84-90.
50. Koltzenburg M, Torebjork HE, Wahren LK. Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. Brain. 1994 Jun;117 ( Pt 3):579-91.
51. Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. Pain. 2009 Sep;145(1-2):96-104.
52. Affaitati G, Costantini R, Fabrizio A, Lapenna D, Tafuri E, Giamberardino MA. Effects of treatment of peripheral pain generators in fibromyalgia patients. Eur J Pain. 2011 Jan;15(1):61-9.
53. Neeck G. Neuroendocrine and hormonal perturbations and relations to the serotonergic system in fibromyalgia patients. Scand J Rheumatol Suppl. 2000;113:8-12.
54. Adler GK, Manfredsdottir VF, Creskoff KW. Neuroendocrine abnormalities in fibromyalgia. Curr Pain Headache Rep. 2002 Aug;6(4):289-98.
55. Valenca MM, Medeiros FL, Martins HA, Massaud RM, Peres MF. Neuroendocrine dysfunction in fibromyalgia and migraine. Curr Pain Headache Rep. 2009 Oct;13(5):358-64.
56. Crofford LJ. The hypothalamic-pituitary-adrenal axis in the pathogenesis of rheumatic diseases. Endocrinol Metab Clin North Am. 2002 Mar;31(1):1-13.
57. McCain GA, Tilbe KS. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J Rheumatol Suppl. 1989 Nov;19:154-7.

58. Griep EN, Boersma JW, de Kloet ER. Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. J Rheumatol. 1993 Mar;20(3):469-74.
59. Cuatrecasas G, Gonzalez MJ, Alegre C, Sesmilo G, Fernandez-Sola J, Casanueva FF, et al. High prevalence of growth hormone deficiency in severe fibromyalgia syndromes. J Clin Endocrinol Metab. 2010 Sep;95(9):4331-7.
60. Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. Curr Pain Headache Rep. 2002 Aug;6(4):259-66.
61. Haas L, Portela LV, Bohmer AE, Oses JP, Lara DR. Increased plasma levels of brain derived neurotrophic factor (BDNF) in patients with fibromyalgia. Neurochem Res. 2010 May;35(5):830-4.
62. Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum. 1994 Nov;37(11):1593-601.
63. Staud R, Domingo M. Evidence for abnormal pain processing in fibromyalgia syndrome. Pain Med. 2001 Sep;2(3):208-15.
64. Gebhart GF. Descending modulation of pain. Neurosci Biobehav Rev. 2004 Jan;27(8):729-37.
65. Bourgoin S, Pohl M, Mauborgne A, Benoliel JJ, Collin E, Hamon M, et al. Monoaminergic control of the release of calcitonin gene-related peptide- and substance P-like materials from rat spinal cord slices. Neuropharmacology. 1993 Jul;32(7):633-40.
66. Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. Arthritis Rheum. 1997 Nov;40(11):1928-39.
67. Martinez-Lavin M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. Semin Arthritis Rheum. 2000 Feb;29(4):197-9.
68. Martinez-Lavin M, Vargas A. Complex adaptive systems allostasis in fibromyalgia. Rheum Dis Clin North Am. 2009 May;35(2):285-98.
69. Straube S, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. Pain. 2009 Jan;141(1-2):10-3.
70. de Rezende Pena C, Grillo LP, das Chagas Medeiros MM. Evaluation of 25-hydroxyvitamin d serum levels in patients with fibromyalgia. J Clin Rheumatol. 2010 Dec;16(8):365-9.
71. Morand EF, Miller MH, Whittingham S, Littlejohn GO. Fibromyalgia syndrome and disease activity in systemic lupus erythematosus. Lupus. 1994 Jun;3(3):187-91.
72. Vitali C, Tavoni A, Neri R, Castrogiovanni P, Pasero G, Bombardieri S. Fibromyalgia features in patients with primary Sjogren's syndrome. Evidence of a relationship with psychological depression. Scand J Rheumatol. 1989;18(1):21-7.
73. Kotter I, Neuscheler D, Gunaydin I, Wernet D, Klein R. Is there a predisposition for the development of autoimmune diseases in patients with fibromyalgia? Retrospective analysis with long term follow-up. Rheumatol Int. 2007 Sep;27(11):1031-9.
74. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology (Oxford). 2001 Jul;40(7):743-9.
75. Togo F, Natelson BH, Adler GK, Ottenweller JE, Goldenberg DL, Struzik ZR, et al. Plasma cytokine fluctuations over time in healthy controls and patients with fibromyalgia. Exp Biol Med (Maywood). 2009 Feb;234(2):232-40.
76. Cordero MD, De Miguel M, Moreno Fernandez AM, Carmona Lopez IM, Garrido Maraver J, Cotan D, et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: implications in the pathogenesis of the disease. Arthritis Res Ther. 2010;12(1):R17.
77. McCarberg BH. Clinical Overview of Fibromyalgia. Am J Ther. 2011 Feb 15;Epub on line.

78. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: comparing the demographic and clinical characteristics in 100 random community cases of fibromyalgia versus controls. J Rheumatol. 1999 Jul;26(7):1577-85.
79. Roizenblatt S, Neto NS, Tufik S. Sleep Disorders and Fibromyalgia. Curr Pain Headache Rep. 2011 May 20;Epub on line.
80. Orellana C, Gratacos J, Galisteo C, Larrosa M. Sexual dysfunction in patients with fibromyalgia. Curr Rheumatol Rep. 2009 Dec;11(6):437-42.
81. Bartley EJ, Rhudy JL, Williams AE. Experimental assessment of affective processing in fibromyalgia. J Pain. 2009 Nov;10(11):1151-60.
82. Salaffi F, Sarzi-Puttini P, Girolimetti R, Atzeni F, Gasparini S, Grassi W. Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. Clin Exp Rheumatol. 2009 Sep-Oct;27(5 Suppl 56):S67-74.
83. Bennett RM, Russell J, Cappelleri JC, Bushmakin AG, Zlateva G, Sadosky A. Identification of symptom and functional domains that fibromyalgia patients would like to see improved: a cluster analysis. BMC Musculoskelet Disord. 2010;11:134.
84. Martinez JE, Ferraz MB, Fontana AM, Atra E. Psychological aspects of Brazilian women with fibromyalgia. J Psychosom Res. 1995 Feb;39(2):167-74.
85. Watson NF, Buchwald D, Goldberg J, Noonan C, Ellenbogen RG. Neurologic signs and symptoms in fibromyalgia. Arthritis Rheum. 2009 Sep;60(9):2839-44.
86. Amris K, Jespersen A, Bliddal H. Self-reported somatosensory symptoms of neuropathic pain in fibromyalgia and chronic widespread pain correlate with tender point count and pressure-pain thresholds. Pain. 2010 Dec;151(3):664-9.
87. Rehm SE, Koroschetz J, Gockel U, Brosz M, Freynhagen R, Tolle TR, et al. A cross-sectional survey of 3035 patients with fibromyalgia: subgroups of patients with typical comorbidities and sensory symptom profiles. Rheumatology (Oxford). 2010 Jun;49(6):1146-52.
88. Ranzolin A, Brenol JCT, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, et al. Association of Concomitant Fibromyalgia With Worse Disease Activity Score in 28 Joints, Health Assessment Questionnaire, and Short Form 36 Scores in Patients With Rheumatoid Arthritis. Arthritis Care & Research. 2009;61(6):794-800.
89. Azevedo VF, Paiva Edos S, Felippe LR, Moreira RA. Occurrence of fibromyalgia in patients with ankylosing spondylitis. Rev Bras Reumatol. 2010 Dec;50(6):646-50.
90. Almodovar R, Carmona L, Zarco P, Collantes E, Gonzalez C, Mulero J, et al. Fibromyalgia in patients with ankylosing spondylitis: prevalence and utility of the measures of activity, function and radiological damage. Clin Exp Rheumatol. 2010 Nov-Dec;28(6 Suppl 63):S33-9.
91. Wilson HD, Robinson JP, Turk DC. Toward the identification of symptom patterns in people with fibromyalgia. Arthritis Rheum. 2009 Apr 15;61(4):527-34.
92. Dadabhoy D, Crofford LJ, Spaeth M, Russell IJ, Clauw DJ, Dadabhoy D, et al. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. Arthritis Res Ther. 2008;10(4):211.
93. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. J Rheumatol. 2009 Oct;36(10):2318-29.
94. Rhudy JL, France CR, Bartley EJ, McCabe KM, Williams AE. Psychophysiological responses to pain: further validation of the nociceptive flexion reflex (NFR) as a measure of nociception using multilevel modeling. Psychophysiology. 2009 Sep;46(5):939-48.
95. Micalos PS, Drinkwater EJ, Cannon J, Arendt-Nielsen L, Marino FE. Reliability of the nociceptive flexor reflex (RIII) threshold and association with Pain threshold. European Journal of Applied Physiology. 2009 Jan;105(1):55-62.

96. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol. 2005 Dec;77(6):353-95.
97. Rhudy JL, Green BA, Arnau RC, France CR. Taxometric analysis of biceps femoris EMG following electrocutaneous stimulation over the sural nerve: Determining the latent structure of the nociceptive flexion reflex (NFR). Int J Psychophysiol. 2008 Jul;69(1):18-26.
98. French DJ, France CR, France JL, Arnott LF. The influence of acute anxiety on assessment of nociceptive flexion reflex thresholds in healthy young adults. Pain. 2005 Apr;114(3):358-63.
99. France CR, al'Absi M, Ring C, France JL, Harju A, Wittmers LE, et al. Nociceptive flexion reflex and pain rating responses during endogenous opiate blockade with naltrexone in healthy young adults. Biol Psychol. 2007 Apr;75(1):95-100.
100. Rhudy JL, Bartley EJ. The effect of the menstrual cycle on affective modulation of pain and nociception in healthy women. Pain. 2010 May;149(2):365-72.
101. Rhudy JL, France CR, Bartley EJ, Williams AE, McCabe KM, Russell JL, et al. Does pain catastrophizing moderate the relationship between spinal nociceptive processes and pain sensitivity? Journal of Pain. [Research Support, Non-U.S. Gov't]. 2009 Aug;10(8):860-9.
102. Edwards L, Ring C, France CR, McIntyre D, Martin U, Edwards L, et al. Effects of opioid blockade on nociceptive flexion reflex thresholds and nociceptive responding in hypertensive and normotensive individuals. Int J Psychophysiol. 2008 Aug;69(2):96-100.
103. Campbell CM, France CR, Robinson ME, Logan HL, Geffken GR, Fillingim RB, et al. Ethnic differences in the nociceptive flexion reflex (NFR). Pain. 2008 Jan;134(1-2):91-6.
104. Gerdelat-Mas A, Simonetta-Moreau M, Thalamas C, Ory-Magne F, Slaoui T, Rascol O, et al. Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. J Neurol Neurosurg Psychiatry. 2007 Oct;78(10):1140-2.
105. Defrin R, Peleg S, Weingarden H, Heruti R, Urca G. Differential effect of supraspinal modulation on the nociceptive withdrawal reflex and pain sensation. Clin Neurophysiol. 2007 Feb;118(2):427-37.
106. Rhudy JL, Williams AE, McCabe KM, Rambo PL, Russell JL. Emotional modulation of spinal nociception and pain: The impact of predictable noxious stimulation. Pain. 2006 Dec;126(1-3):221-33.
107. Mylius V, Kunz M, Schepelmann K, Lautenbacher S, Mylius V, Kunz M, et al. Sex differences in nociceptive withdrawal reflex and pain perception. Somatosens Mot Res. 2005 Sep;22(3):207-11.
108. Goffaux P, de Souza JB, Potvin S, Marchand S. Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. Pain. 2009 Sep;145(1-2):18-23.
109. France CR, Rhudy JL, McGlone S. Using normalized EMG to define the nociceptive flexion reflex (NFR) threshold: further evaluation of standardized NFR scoring criteria. Pain. 2009 Sep;145(1-2):211-8.
110. Rhudy JL, France CR. Defining the nociceptive flexion reflex (NFR) threshold in human participants: a comparison of different scoring criteria. Pain. 2007 Apr;128(3):244-53.
111. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain. 2004 Jan;107(1-2):7-15.
112. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol. 2010 Oct;6(10):599-606.
113. Price DD, Staud R, Robinson ME, Mauderli AP, Cannon R, Vierck CJ, et al. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. Pain. 2002 Sep;99(1-2):49-59.
114. Staud R, Robinson ME, Price DD, Staud R, Robinson ME, Price DD. Temporal summation of second pain and its maintenance are useful for characterizing widespread central sensitization of fibromyalgia patients. Journal of Pain. [Research Support, N.I.H., Extramural]. 2007 Nov;8(11):893-901.

115. Staud R, Price DD, Robinson ME, Mauderli AP, Vierck CJ, Staud R, et al. Maintenance of windup of second pain requires less frequent stimulation in fibromyalgia patients compared to normal controls. Pain. 2004 Aug;110(3):689-96.
116. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010 Aug;62(8):2545-55.
117. Nebel MB, Gracely RH. Neuroimaging of fibromyalgia. Rheum Dis Clin North Am. 2009 May;35(2):313-27.
118. Hargrove JB, Bennett RM, Simons DG, Smith SJ, Nagpal S, Deering DE. Quantitative electroencephalographic abnormalities in fibromyalgia patients. Clin EEG Neurosci. 2010 Jul;41(3):132-9.
119. Assumpcao A, Pagano T, Matsutani LA, Ferreira EA, Pereira CA, Marques AP. Quality of life and discriminating power of two questionnaires in fibromyalgia patients: Fibromyalgia Impact Questionnaire and Medical Outcomes Study 36-Item Short-Form Health Survey. Rev Bras Fisioter. 2010 Jul-Aug;14(4):284-9.
120. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Arthritis & Rheumatism. 1990 Feb;33(2):160-72.
121. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia Criteria and Severity Scales for Clinical and Epidemiological Studies: A Modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011 Feb 1;Epub on line.
122. Paiva ES, Jones KD. Rational treatment of fibromyalgia for a solo practitioner. Best Pract Res Clin Rheumatol. 2010 Jun;24(3):341-52.
123. Carville SF, Arendt-Nielsen S, Bliddal H, Blotman F, Branco JC, Buskila D, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008 Apr;67(4):536-41.
124. Moretti FA, Heymann RE, Marvulle V, Pollak DF, Riera R. Assessing knowledge on fibromyalgia among internet users. Rev Bras Reumatol. 2011 Feb;51(1):7-19.
125. Hauser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome - a systematic review. Eur J Pain. 2009 Jan;14(1):5-10.
126. Di Franco M, Iannuccelli C, Atzeni F, Cazzola M, Salaffi F, Valesini G, et al. Pharmacological treatment of fibromyalgia. Clin Exp Rheumatol. 2011 Nov-Dec;28(6 Suppl 63):S110-6.
127. Roskell NS, Beard SM, Zhao Y, Le TK. A Meta-Analysis of Pain Response in the Treatment of Fibromyalgia. Pain pract. 2010 Dec 28.
128. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain. 2010 Jun;11(6):505-21.
129. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA. 2009 Jan 14;301(2):198-209.
130. Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford). 2010 Apr;49(4):706-15.
131. Vlainich R, Issy AM, Gerola LR, Sakata RK. Effect of intravenous lidocaine on manifestations of fibromyalgia. Pain pract. 2010 Jul-Aug;10(4):301-5.
132. Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG. Psychological treatments for fibromyalgia: A meta-analysis. Pain. 2010 Aug 18.
133. Bernardy K, Fuber N, Kollner V, Hauser W. Efficacy of Cognitive-Behavioral Therapies in Fibromyalgia Syndrome - A Systematic Review and Metaanalysis of Randomized Controlled Trials. J Rheumatol. 2010 Aug 3.
134. Beck AT. Thinking and depression II. Theory and therapy. Arch Gen Psychiatry. 1964 Jun;10:561-71.

135. Hassett AL, Gevirtz RN. Nonpharmacologic treatment for fibromyalgia: patient education, cognitive-behavioral therapy, relaxation techniques, and complementary and alternative medicine. Rheum Dis Clin North Am. 2009 May;35(2):393-407.
136. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, et al. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain. [Research Support, U.S. Gov't, Non-P.H.S.]. 2004 Apr;127(Pt 4):835-43.
137. Edwards RR, Bingham CO, 3rd, Bathon J, Haythornthwaite JA, Edwards RR, Bingham CO, 3rd, et al. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. Arthritis & Rheumatism. [Review]. 2006 Apr 15;55(2):325-32.
138. Hassett AL, Cone JD, Patella SJ, Sigal LH. The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. Arthritis Rheum. 2000 Nov;43(11):2493-500.
139. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev. 2006 Jan;26(1):17-31.
140. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry. 2008 Apr;69(4):621-32.
141. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. Psychosom Med. 2004 Nov-Dec;66(6):837-44.
142. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. Health Psychol. 2007 Jan;26(1):1-9.
143. Nielson WR, Walker C, McCain GA. Cognitive behavioral treatment of fibromyalgia syndrome: preliminary findings. J Rheumatol. 1992 Jan;19(1):98-103.
144. Mengshoel AM, Forseth KO, Haugen M, Walle-Hansen R, Forre O. Multidisciplinary approach to fibromyalgia. A pilot study. Clin Rheumatol. 1995 Mar;14(2):165-70.
145. Goldenberg DL. Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome. Curr Opin Rheumatol. 1994 Mar;6(2):223-33.
146. Thieme K, Flor H, Turk DC. Psychological pain treatment in fibromyalgia syndrome: efficacy of operant behavioural and cognitive behavioural treatments. Arthritis Res Ther. 2006;8(4):R121.
147. Falcão D, Sales L, Leite J, Feldman D, Valim V, Natour J. Cognitive Behavioral Therapy for the Treatment of Fibromyalgia Syndrome: A Randomized Controlled Trial. Journal of Musculoskeletal Pain. 2008;16(3):133-40.
148. van Koulil S, Effting M, Kraaimaat FW, van Lankveld W, van Helmond T, Cats H, et al. Cognitive-behavioural therapies and exercise programmes for patients with fibromyalgia: state of the art and future directions. Annals of the Rheumatic Diseases. 2007 May;66(5):571-81.
149. Sanudo B, Galiano D, Carrasco L, Blagojevic M, de Hoyo M, Saxton J. Aerobic exercise versus combined exercise therapy in women with fibromyalgia syndrome: a randomized controlled trial. Arch Phys Med Rehabil. 2010 Dec;91(12):1838-43.
150. Kayo AH, Peccin MS, Sanches CM, Trevisani VF. Effectiveness of physical activity in reducing pain in patients with fibromyalgia: a blinded randomized clinical trial. Rheumatol Int. 2011 May 19;Epub on line.
151. Assumpcao A, Sauer JF, Mango PC, Pascual Marques A. Physical function interfering with pain and symptoms in fibromyalgia patients. Clin Exp Rheumatol. 2010 Nov-Dec;28(6 Suppl 63):S57-63.
152. Langhorst J, Musial F, Klose P, Hauser W. Efficacy of hydrotherapy in fibromyalgia syndrome--a meta-analysis of randomized controlled clinical trials. Rheumatology (Oxford). 2009 Sep;48(9):1155-9.
153. Gowans SE. Fibromyalgia: Increased regular physical activity as 'exercise' in fibromyalgia. Nat Rev Rheumatol. 2010 Sep;6(9):499-500.
154. Fontaine KR, Conn L, Clauw DJ. Effects of lifestyle physical activity on perceived symptoms and physical function in adults with fibromyalgia: results of a randomized trial. Arthritis Res Ther. 2010;12(2):R55.

155. Culos-Reed SN, Brawley LR. Fibromyalgia, physical activity, and daily functioning: the importance of efficacy and health-related quality of life. Arthritis Care Res. 2000 Dec;13(6):343-51.
156. Iversen MD, Hammond A, Betteridge N. Self-management of rheumatic diseases: state of the art and future perspectives. Ann Rheum Dis. 2010 Jun;69(6):955-63.
157. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ, Arthritis Research Campaign working group on c, et al. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. Rheumatology (Oxford). 2010 Jun;49(6):1063-8.
158. Mendonca ME, Santana MB, Baptista AF, Datta A, Bikson M, Fregni F, et al. Transcranial DC Stimulation in Fibromyalgia: Optimized Cortical Target Supported by High-Resolution Computational Models. J Pain. 2011 May;12(5):610-7.
159. Heymann RE, Paiva Edos S, Helfenstein M, Jr., Pollak DF, Martinez JE, Provenza JR, et al. Brazilian consensus on the treatment of fibromyalgia. Rev Bras Reumatol. 2010 Feb;50(1):56-66.
160. Hauser W, Bernardy K, Arnold B, Offenbacher M, Schiltenwolf M. Efficacy of multicomponent treatment in fibromyalgia syndrome: A meta-analysis of randomized controlled clinical trials. Arthritis Rheum. 2009 Feb 15;61(2):216-24.
161. Markkula R, Kalso E, Huunan-Seppala A, Koskenvuo M, Koskenvuo K, Leino-Arjas P, et al. The burden of symptoms predicts early retirement: A twin cohort study on fibromyalgia-associated symptoms. Eur J Pain. 2011 Feb 10.
162. Edwards RR, Calahan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol. 2011 Apr;7(4):216-24.
163. Moore RA, Straube S, Paine J, Phillips CJ, Derry S, McQuay HJ. Fibromyalgia: Moderate and substantial pain intensity reduction predicts improvement in other outcomes and substantial quality of life gain. Pain. 2010 May;149(2):360-4.
164. de Souza JB, Potvin S, Goffaux P, Charest J, Marchand S. The deficit of pain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. Clinical Journal of Pain. 2009 Feb;25(2):123-7.
165. Goldenberg DL. Pain/Depression dyad: a key to a better understanding and treatment of functional somatic syndromes. Am J Med. 2010 Aug;123(8):675-82.
166. Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain. Front Biosci. 2009;14:5291-338.
167. Wolfe F, Russell IJ, Vipraio G, Ross K, Anderson J. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. J Rheumatol. 1997 Mar;24(3):555-9.
168. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety. 2000;12 Suppl 1:2-19.
169. Klauenberg S, Maier C, Assion HJ, Hoffmann A, Krumova EK, Magerl W, et al. Depression and changed pain perception: hints for a central disinhibition mechanism. Pain. 2008 Nov 30;140(2):332-43.
170. Glass JM. Review of cognitive dysfunction in fibromyalgia: a convergence on working memory and attentional control impairments. Rheum Dis Clin North Am. 2009 May;35(2):299-311.
171. Clauw DJ. Pain management: Fibromyalgia drugs are 'as good as it gets' in chronic pain. Nat Rev Rheumatol. 2010 Aug;6(8):439-40.
172. Emery CF, France CR, Harris J, Norman G, Vanarsdalen C. Effects of progressive muscle relaxation training on nociceptive flexion reflex threshold in healthy young adults: a randomized trial. Pain. 2008 Aug 31;138(2):375-9.
173. Ang DC, Chakr R, Mazzuca S, France CR, Steiner J, Stump T. Cognitive-behavioral therapy attenuates nociceptive responding in patients with fibromyalgia: a pilot study. Arthritis Care Res (Hoboken). 2010 May;62(5):618-23.

5. ARTIGO CIENTÍFICO (173)

# Cognitive–Behavioral Therapy Attenuates Nociceptive Responding in Patients With Fibromyalgia: A Pilot Study

DENNIS C. ANG,1 RAFAEL CHAKR,1 STEVE MAZZUCA,1 CHRISTOPHER R. FRANCE,2 JENNIFER STEINER,1 AND TIMOTHY STUMP1

*Objective.* To explore the possibility that cognitive–behavioral therapy (CBT) influences fibromyalgia symptoms via descending inhibition of nociception, we evaluated the effects of CBT on the nociceptive flexion reflex (NFR) threshold, an objective measure of spinal nociceptive transmission.
*Methods.* Female fibromyalgia patients (n = 32) were randomized to 6 weekly sessions of telephone-delivered CBT or usual care (UC). Assessments of the NFR threshold and clinical outcomes were conducted at baseline, week 6 (post-CBT), and week 12.
*Results.* From baseline to week 6, the NFR threshold increased in the CBT group and decreased in the UC group (mean ± SD 4.4 ± 13.7 mA versus -10.2 ± 9.9 mA; $P = 0.005$). This difference was also apparent at week 12 (mean ± SD 7.3 ± 9.2 mA for CBT versus -5.4 ± 13.5 mA for UC; $P = 0.01$). The groups reported similar reductions in NFR pain ratings at week 6 (mean ± SD -20.2 ± 23.9 for CBT versus -14.9 ± 16.4 for UC; $P = 0.8$) and week 12 (mean ± SD -8.9 ± 25.3 for CBT versus -10.8 ± 24.1 for UC; $P = 0.4$).
*Conclusion.* Compared with UC, CBT reduced nociceptive responding in fibromyalgia patients. Moreover, while the UC group exhibited longitudinal decreases in both the stimulation level and pain associated with the NFR threshold, those receiving CBT required more intense stimulation to elicit the NFR as well as rated that stimulation as less painful than at baseline. These data indicate the need for a larger study to confirm that changes in nociceptive responsivity may underlie the benefits of CBT in fibromyalgia patients.

ClinicalTrials.gov identifier: NCT00965601.
1Dennis C. Ang, MD, MS, Rafael Chakr, MD, Steve Mazzuca, PhD, Jennifer Steiner, BA, Timothy Stump, MA: Indiana University, Indianapolis; 2Christopher R. France, PhD: Ohio University, Athens.

**INTRODUCTION**

Fibromyalgia (FM) is a chronic disabling syndrome affecting 2% of the general population and is 7-fold more prevalent among women than men (1). FM is characterized by diffuse tenderness and musculoskeletal pain and discomfort on palpation of specific sites known as tender points (2). While the exact cause of FM is yet to be fully understood, our understanding of FM is increasingly focused on central sensitization (CS) (3). CS, which originates from hyperexcitability of the dorsal horn neurons in the spinal cord, is manifested in below-average endogenous paininhibitory capacity and above-average sensitivity to pain (4).

FM, as yet incurable, must be managed as a chronic illness. Treatment approaches include both pharmacologic and nonpharmacologic therapies. Cognitive–behavioral therapy (CBT) has been shown to be efficacious for managing the symptoms of FM (5,6). The rationale for using CBT in treating chronic pain stems from the assumption that the experience of pain is the result of complex interplay involving pathophysiology, cognition, affect, and behavior (7). Modification of any one of these 4 factors can positively or negatively affect the course of an individual's pain experience. Several psychological models (e.g., social cognitive theory) have been proposed to explain the mechanisms by which CBT helps patients with FM (8). However, to better understand how CBT works, attention should also be paid to underlying biologic mechanisms. For example, it is possible that CBT may reduce physiologic pain sensitivity. Accordingly, efforts to investigate the effect of CBT on biologic parameters may provide a theorybased model for developing new treatment approaches and raise testable hypotheses for novel mechanisms of action of CBT.

The nociceptive flexion reflex (NFR) is a neurophysiologic phenomenon that represents responsivity to noxious stimulation via elicitation of a spinal withdrawal reflex upon stimulation of a sensory nerve (9). The level of stimulation required to elicit this reflex can be used as an objective measure of nociception in humans, and permits exploration of pain processing pathways at spinal and supraspinal levels (10,11). Consistent with the notion of heightened pain sensitivity in FM, 2 prior studies have reported lower NFR thresholds (or heightened nociceptive responsivity) among volunteers with FM compared with healthy controls (12,13). Because heightened sensitivity to noxious stimuli is thought to be a pathologic hallmark of FM, we hypothesized that CBT, as an adjunct

treatment to usual care (UC), would result in the lowering of the nociceptive responding, as evidenced by an increase in the NFR threshold.

## SUBJECTS AND METHODS

In a 12-week randomized controlled trial of CBT versus UC in patients with FM, we measured the NFR threshold as a primary outcome. Secondary (clinical) measures included self-reported pain and physical impairment. Study procedures, including written informed consent, were approved by the Institutional Review Board of Indiana University-Purdue University, Indianapolis.

**Subjects.** All subjects met the American College of Rheumatology classification criteria for FM (2). A rheumatologist (DCA) confirmed the diagnosis of FM. To be eligible, subjects had to be moderately symptomatic with respect to pain intensity (Fibromyalgia Impact Questionnaire [FIQ] pain score ≥3, and FIQ physical impairment [FIQ PI] score ≥2) (14), as well as be taking stable doses of pain-related medications (i.e., antidepressants, tricyclic antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs [NSAIDs], and opiates) for at least 4 weeks. To reduce the confounding effect of sex, we enrolled only female subjects. We excluded subjects who had peripheral neuropathy, diabetes mellitus, demyelinating disorders, and inflammatory rheumatic diseases.

**Procedures.** Subjects who satisfied the above eligibility criteria and gave written informed consent were randomized to 1 of 2 treatment arms: 6 weekly sessions of CBT in addition to UC, or UC alone. CBT was delivered over the telephone during weeks 1–6 by a single trained therapist (psychology graduate student). The therapist followed a manualized treatment protocol (15), and subjects received the companion workbook to encourage active participation during the treatment session (16). Treatment sessions were typically 30–40 minutes long. Components of CBT intervention included time-contingent activity pacing, pleasant activity scheduling, relaxation, automatic thoughts and pain, cognitive restructuring, and stress management. On the other hand, UC consisted of customary care received from the subjects' treating physicians.

Prior to the intervention, the therapist was trained in CBT in a classroom environment and received further training through videotapes and textbooks. Throughout the study, the therapist was under the supervision of a clinical psychologist. After listening to the audiotapes of the recorded therapy sessions, the clinical psychologist provided guidance and instructions to the therapist if any drift from the intervention protocols occurred. Additionally, each participant's progress was discussed during the weekly supervision sessions.

All study participants were allowed to continue with their pain-related medications throughout the 12-week study period. To reduce the confounding effects of drugs on the NFR threshold values, subjects were asked to stay on the same pain-related medication regimen (including dosing) throughout the study period. In addition, subjects underwent a 48-hour washout of any NSAIDs prior to the NFR test. Subjects were asked also to avoid any pro re nata medications (e.g., hydrocodone, acetaminophen, etc.) for at least 6 hours prior to the NFR test. To ensure compliance with drug restriction, subjects were required to complete a drug diary (paper format) throughout the study. Based on the drug diary report, one subject failed to comply with the 48-hour NSAIDs washout, and another subject with the pro re nata medication restriction. The former subject was asked to return 2 days later for the assessment, and the latter subject was rescheduled for the following day.

Participants were assessed at baseline, week 6 (post-CBT), and week 12 of the study time line. Assessments included the NFR threshold and completion of Web-based self-administered clinical measures. Participants were scheduled for their followup assessments at the same time of the day as they were at study entry. The NFR tester was blinded to the group assignment.

**Assessment of NFR threshold.** The NFR threshold assessment was performed according to a standardized, validated protocol (17). In summary, repeated electrocutaneous stimulation was applied to the sural nerve. Using an up-down staircase method, stimulation intensity began at 0 mA and increased in 4-mA increments until detection of the first reflex. The NFR was considered to be elicited if the mean electromyogram (EMG) response from same-leg biceps femoris in the 90–150-msec poststimulation interval exceeded the mean EMG activity during the 60-msec prestimulation baseline interval (-65 to -5 msec) by at least 1.37 SDs. After detection of the first NFR, the stimulation intensity was reduced by 2 mA until the reflex disappeared. Thereafter, the stimulation intensity was adjusted upward and downward in 1-mA increments until the NFR appeared and disappeared 2 more times. The NFR threshold (expressed in mA) was the average of peaks and troughs of the stimulation intensities surrounding the second and third occurrence of the NFR. Hence, higher NFR threshold values indicate that higher stimulus intensities were required to evoke a consistent reflex response. During the NFR threshold test, participants rated the pain sensation of each electrical stimulus using a scale of 0–100, where 0 = no pain and 100 = extremely painful. The NFR pain rating was the mean pain rating at which the NFR was detected.

**Clinical measures.** The FIQ is a disease-specific composite measure to determine the spectrum of problems related to FM (14). Widely used in FM clinical trials, the FIQ total includes the FIQ PI subscale, 6 visual analog scales for measuring pain (FIQ pain), sleep, anxiety, morning stiffness, and depression, and 2 one-item questions for work status and overall well-being. The scoring of the FIQ total (scale 0–100) is such that a higher score indicates a greater impact of FM on the person. Bennett et al have reported that a 14% change in the FIQ total over 12 weeks is likely to be clinically meaningful (18).

The FIQ PI is a 10-item subscale of the FIQ total that inquires about the participant's ability to do 11 different types of physical activity, with each item rated on a 4-point Likert-type scale. The range of the score is between 0 and 10, where a higher score indicates a negative impact. The FIQ PI correlates well ($r = 0.65$) with the Arthritis Impact Measurement Scale lower extremity physical function scale (19). In a trial of pool therapy and education, Mannerkorpi et al found the FIQ PI to be responsive, and it correlated with improvement in the 6-minute walk test (20,21).

The Patient Health Questionnaire 8-item depression scale (PHQ-8) is a brief self-administered scale that assesses major depressive disorder core symptoms and allows a score (range 0–24) based on the total number and severity of depressive symptoms noted over the previous 2-week period (22,23). A PHQ-8 score ≥10 represents clinically significant depression (22).

**Statistical analysis.** To compare treatment groups with respect to baseline characteristics, we used *t*-tests for continuous variables and chi-square tests (or Fisher's exact test, if appropriate) for categorical variables. We used a mixed-effects linear model (i.e., repeated-measures) approach to compare treatment groups with respect to the change in the NFR threshold and the pain rating at the NFR threshold. The model included a random subject effect and fixed effects for treatment group, visit (i.e., week 6 or week 12), the treatment group-visit interaction, baseline NFR threshold (or NFR pain rating), and study entry medications. The same approach was also used to compare treatment groups with respect to clinical measures (i.e., FIQ PI, PHQ-8, and FIQ pain). Finally, for the proportion of subjects who reported a clinically meaningful (14%) improvement in total FIQ scores at week 12, we used Fisher's exact test.

## RESULTS

Between August 2008 and March 2009, 111 patients referred from the community rheumatology clinic offices were screened for inclusion in the study (Figure 1). Of these, 32 (29%) met the eligibility criteria and were randomly assigned to receive telephone-based CBT (n = 17) or UC (n = 15). Four participants (12.5%) did not complete the week 6 and week 12 study assessments: 2 refused further followup (1 from each group) and 2 stated that the NFR assessment was too painful (1 from each group). In terms of sociodemographic and clinical characteristics, these 4 subjects were not significantly different from the 28 participants who completed the study.

Baseline characteristics of subjects randomized to the 2 treatment arms are presented in Table 1. The 32 female participants had a mean ± SD age of 49 ± 11 years, 78% were white, 66% had a high school education or more, and 41% were employed. At baseline, the sample had a mean ± SD disease duration of 12 ± 6 years, 15 (46%) were taking opioid analgesics, 9 (28%) were taking anticonvulsants, and 22 (69%) were taking an antidepressant (excluding tricyclic antidepressants). Based on the PHQ-8 (score ≥ 10), 18 (56%) of the participants had clinically significant depression. Regarding illness severity, the mean ± SD FIQ total score was 65 ± 14, suggesting a moderate to severely ill patient population. For self-report clinical pain, the mean ± SD FIQ pain score was 8 ± 2. There were no significant differences at baseline between the 2 treatment arms with respect to sociodemographic variables, clinical characteristics, NFR threshold, and prior use of nondrug therapies (e.g., physical therapy, chiropractor, massage, and psychologist). With respect to study entry medications, there were no significant differences between the 2 treatment arms, except for the use of NSAIDs. Compared with the UC group, more subjects in the CBT groups were taking NSAIDs at baseline (76% versus 26%; $P = 0.01$).

Compared with UC, CBT resulted in marginal improvements in FIQ PI scores at week 6 (mean ± SD = 0.3 ± 2.2 versus 0.2 ± 1.7; adjusted $P = 0.5$) and at week 12 (mean ± SD -0.6 ± 2.3 versus 0.5 ± 1.2; adjusted $P = 0.13$), which reflects an overall treatment effect of moderate size (effect size [ES] = 0.5 pooled SD). Although the improvement in FIQ pain at week 6 was no different between the 2 comparator groups (mean ± SD - 0.2 ± 1.8 versus -0.3 ± 1.6; adjusted $P = 0.8$), there was a suggestion of separation favoring CBT over UC at week 12 (mean ± SD -0.6 ± 1.6 versus -0.3 ± 1.7; adjusted $P = 0.6$); however, the overall effect was small (ES = 0.2). Additionally, subjects in the CBT group were twice as likely to report a clinically meaningful improvement in the FIQ total (33% versus 15%; $P = 0.3$) at week 12 than subjects in the UC group (ES = 0.6). On the other hand, there was no meaningful betweengroup difference in the change in PHQ-8 depression scores from baseline to week 12 (mean ± SD -0.9 ± 5.2 versus 0.0 ± 4.1; adjusted $P = 0.8$).

The overall effect of CBT on the NFR threshold was highly significant ($P = 0.002$). A summary of changes in the NFR thresholds over both intervals is shown in Table 2. From baseline to week 6, the CBT group exhibited a mean ± SD increase in the NFR threshold of 4.4 ± 13.7 mA, while the UC group showed a mean ± SD decrease over the same interval (-10.2 ± 9.9 mA; $P = 0.005$). This difference was also apparent, and remained significant, at week 12 (7.3 ± 9.2 mA versus -5.4 ± 13.5 mA; $P = 0.01$). Interestingly, while both groups reported reduction in their NFR pain ratings, there were no statistically significant between-group differences at either the week 6 ($P = 0.8$) or week 12 ($P = 0.4$) time point.

## DISCUSSION

In this pilot study, a 6-week program of telephone-administered

CBT was associated with an increase in the NFR threshold, indicating diminished responsivity to noxious stimulation at the week 6 and week 12 study visits. In contrast, subjects in the UC group had a decrease in the NFR threshold, suggesting greater responsivity (or more sensitivity) to noxious stimulation at both study visits. Although there were no significant between-group differences in NFR pain ratings, the groups received very different levels of stimulation to elicit the NFR. In the CBT group, while the NFR pain rating was going down, the NFR threshold was going up. That is, while reporting the experience as being less painful over time, the CBT group was enduring more intense stimulation to elicit the NFR. Similarly, the UC group was also reporting the experience as being less painful; however, at a significantly less intense stimulation. These findings are consistent with prior evidence of acute increases in the NFR threshold following brief coping skills training in healthy young adults (24) and older adults with osteoarthritis (25). To further explore novel mechanisms through which cognitive interventions might improve patient outcomes, our data indicate the need for a larger attention-controlled trial to determine if CBT works via changing the nociceptive responsivity, as reflected in the NFR.

The NFR is mediated by an anatomic substrate composed of a complex network of interneurons that are primarily located at the spinal level (9). In turn, these spinal interneurons are modulated by supraspinal influences from the cerebral cortex, cerebellum, basal ganglia, and brainstem. In spinal cord–injured humans, Dimitrijevic and Nathan have reported abnormal excitability of the NFR, suggesting that a tonic inhibitory modulation by several supraspinal pathways is present in normal subjects (26). Therefore, a lack of descending inhibitory control may result in increased sensitivity of the spinal reflex loop, reinforcing the suggestion that the NFR can be dynamically controlled by the brain (9,27). The current study raises the possibility that by altering thought processes CBT may influence nociception by activating (or reactivat-ing) descending inhibitory pathways to reduce nociceptive transmission within the spinal cord.

Two important limitations of this study must be taken into account. First, although the sample recruited for this trial was sufficient to detect an effect of CBT on the NFR threshold, a significant effect of CBT on clinical symptoms would have required a significantly larger sample. Given the effect sizes (FIQ pain = 0.2, FIQ PI = 0.5, and FIQ total = 0.6) noted in our study, at least 45 subjects per group (a total of 90) are needed to detect a statistically significant difference in any one of the clinical outcome measures. Nevertheless, the effect sizes noted in our study are consistent with the published literature. In a recent meta-analysis, Eccleston et al have reported that the effect size of CBT on pain was 0.19 and on disability was 0.7 (28). Moreover, it is important to note that the changes in the clinical symptoms (particularly, FIQ PI) observed in the treatment groups favored CBT over UC; group differences at weeks 6 and 12 were similar in magnitude to those seen in previous nonpharmacologic trials in this population (21,29), the lack of statistical significance notwithstanding. The lack of statistical significance could also be attributed to our short followup period (i.e., 6 weeks after program completion). There is evidence from the literature showing that benefits from CBT are observed only after 3–6 months (i.e., delayed effect) after program completion (5,7,30).

Second, because we allowed subjects to continue with their pain-related medications (including opiates and antidepressants), medications could bias the study results. For example, opiates have been shown to reduce nociceptive responsivity (i.e., increase the NFR threshold) by acting directly on the spinal transmission of nociceptive signals (31,32). Sandrini et al also demonstrated an

increase in the NFR threshold using amitriptyline (33). Although medications could reset the NFR threshold values at study entry, the changes in the NFR threshold during the 12-week study cannot be attributed to drugs because no substantial changes in the subjects' medication regimens were reported during the entire length of the study. One subject in the CBT arm had to discontinue a study entry medication (trazodone), and one UC subject initiated a new drug (cyclobenzaprine). In theory, the latter drug changes on both arms should actually minimize, rather than magnify, the difference in the NFR threshold noted in our study. To reduce the potential bias with self-report use of medication, future study should use an electronic drug diary to ensure a more accurate collection of drug intake history.

Our study is important because, to our knowledge, this is the first study to offer evidence of a biologic effect of a psychological-based therapy in the management of chronic FM pain. In contrast with other evoked pain measures (e.g., pressure pain threshold), the NFR provides an indicator of nociception that is typically correlated with subjective pain threshold, but is distinct in its ability to provide an objective measure of spinal modulation of nociceptive transmission (9). Future investigation should determine definitively whether changes in the NFR threshold (or nociceptive responsivity) mediate improvement in clinical symptoms.

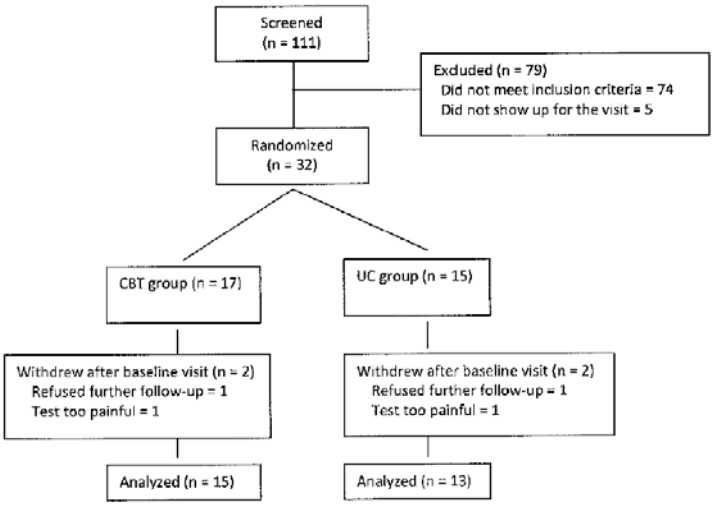


**Figure 1.** Flow of participants through the trial. CBT = cognitive–behavioral therapy; UC = usual care.

**Table 1. Baseline characteristics of subjects***

| Characteristic | Treatment group | |
|---|---|---|
| | CBT (n = 17) | UC (n = 15) |
| Age, years | 50.5 ± 9.5 | 47.0 ± 12.4 |
| White, % | 81 | 80 |
| Education >12 years, % | 70 | 60 |
| Married, % | 59 | 40 |
| Employed, % | 53 | 27 |
| Comfortable with income, % | 7 | 28 |
| Duration of fibromyalgia, years | 11.8 ± 4.6 | 12.3 ± 7.9 |
| PHQ-8, range 0–24† | 10 ± 5.4 | 13 ± 4.5 |
| FIQ PI, range 0–10† | 5.6 ± 1.8 | 5.4 ± 1.7 |
| FIQ pain, range 0–10† | 7.6 ± 1.8 | 7.8 ± 1.4 |
| FIQ total, range 0–100† | 62.2 ± 15 | 67.8 ± 12 |
| Taking antidepressants, %‡ | 76 | 60 |
| Taking tricyclic antidepressants, %§ | 6 | 20 |
| Taking anticonvulsants, % | 23 | 33 |
| Taking opiates, % | 52 | 40 |
| Taking NSAIDs, %¶ | 76 | 26 |

* Values are the mean ± SD unless otherwise stated. CBT = cognitive–behavioral therapy; UC = usual care; PHQ-8 = Patient Health Questionnaire 8-item depression scale; FIQ PI = Fibromyalgia Impact Questionnaire physical impairment; NSAIDs = nonsteroidal antiinflammatory drugs.
† Higher scores reflect more severe symptoms.
‡ All other antidepressants other than tricyclic agents.
§ Gabapentin and pregabalin.
¶ $P = 0.01$.

Table 2. Baseline and changes in NFR threshold and pain rating at NFR threshold at weeks 6 and 12*

| | No. of patients | | NFR threshold, mean ± SD mA | | Pain, mean ± SD† | |
|---|---|---|---|---|---|---|
| | CBT | UC | CBT | UC | CBT | UC |
| Baseline values | 17 | 15 | 32.5 ± 15 | 37.6 ± 10 | 56.3 ± 30.5 | 45.3 ± 24.5 |
| Week 6 change‡ | 15 | 13 | 4.4 ± 13.7 | −10.2 ± 9.9 | −20.2 ± 23.9 | −14.9 ± 16.4 |
| Week 12 change‡ | 15 | 13 | 7.3 ± 9.2 | −5.4 ± 13.5 | −8.9 ± 25.3 | −10.8 ± 24.1 |

* NFR = nociceptive flexion reflex; CBT = cognitive–behavioral therapy; UC = usual care.
† Pain rating at NFR threshold, where 0 = no pain and 100 = extremely painful.
‡ Change in reference to baseline measurement.

**ARTICLE REFERENCES**


1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19–28.
2. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33: 160–72.
3. Price DD, Staud R. Neurobiology of fibromyalgia syndrome. J Rheumatol Suppl 2005;75:22–8.
4. Staud R, Smitherman ML. Peripheral and central sensitization in fibromyalgia: pathogenetic role. Curr Pain Headache Rep 2002;6:259–66.
5. Cedraschi C, Desmeules J, Rapiti E, Baumgartner E, Cohen P, Finckh A, et al. Fibromyalgia: a randomised, controlled trial of a treatment programme based on self management. Ann Rheum Dis 2004;63:290–6.
6. Williams DA, Cary MA, Groner KH, Chaplin W, Glazer LJ, Rodriguez AM, et al. Improving physical functional status in patients with fibromyalgia: a brief cognitive behavioral intervention. J Rheumatol 2002;29:1280–6.
7. Williams DA. Psychological and behavioural therapies in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003;17:649–65.
8. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LM. Psychological aspects of persistent pain: current state of the science. J Pain 2004;5:195–211. 9. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005;77:353–95.
10. Sandrini G, Ruiz L, Capararo M, Danilov A, Beretta A, Nappi G. Effects of dothiepin on nociceptive flexion reflex and diffuse noxious inhibitory controls in humans. Eur J Pharmacol 1993;243:99–102.
11. Sandrini G, Arrigo A, Bono G, Nappi G. The nociceptive flexion reflex as a tool for exploring pain control systems in headache and other pain syndromes. Cephalalgia 1993;13: 21–7.
12. Banic B, Petersen-Felix S, Andersen OK, Radanov BP, Villiger PM, Arendt-Nielsen L, et al. Evidence for spinal cord hypersensitivity in chronic pain after whiplash injury and in fibromyalgia. Pain 2004;107:7–15.
13. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 2003;48:1420–9.
14. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005;23 Suppl 39: S154–62.
15. Otis J. Managing chronic pain: a cognitive-behavioral therapy approach (therapist guide). New York: Oxford University; 2007.
16. Otis J. Managing chronic pain: a cognitive-behavioral therapy approach (workbook). New York: Oxford University; 2007.
17. Rhudy JL, France CR. Defining the nociceptive flexion reflex (NFR) threshold in human participants: a comparison of different scoring criteria. Pain 2007;128:244–53.
18. Bennett RM, Bushmakin AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol 2009;36: 1304–11.
19. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728–33.
20. Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome: a prospective, randomized study. J Rheumatol 2000;27:2473–81.
21. Mannerkorpi K, Ahlmen M, Ekdahl C. Six- and 24-month follow-up of pool exercise therapy and education for patients with fibromyalgia. Scand J Rheumatol 2002;31:306–10.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16: 606–13.
23. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr Ann 2002;32:1–7.
24. Emery CF, France CR, Harris J, Norman G, Vanarsdalen C. Effects of progressive muscle relaxation training on nociceptive flexion reflex threshold in healthy young adults: a randomized trial. Pain 2008;138:375–9.
25. Emery CF, Keefe FJ, France CR, Affleck G, Waters S, Fondow MD, et al. Effects of a brief coping skills training intervention on nociceptive flexion reflex threshold in patients having osteoarthritic knee pain: a preliminary laboratory study of sex differences. J Pain Symptom Manage 2006;31:262–9.
26. Dimitrijevic MR, Nathan PW. Studies of spasticity in man. 3. Analysis of reflex activity evoked by noxious cutaneous stimulation. Brain 1968;91:349–68.
27. Andersen OK, Finnerup NB, Spaich EG, Jensen TS, Rendt-Nielsen L. Expansion of nociceptive withdrawal reflex receptive fields in spinal cord injured humans. Clin Neurophysiol 2004;115:2798–810.
28. Eccleston C, Williams AC, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2009;2:CD007407.
29. Burckhardt CS, Mannerkorpi K, Hedenberg L, Bjelle A. A randomized, controlled clinical trial of education and physical training for women with fibromyalgia. J Rheumatol 1994; 21:714–20.

30. Turner JA, Clancy S. Comparison of operant behavioral and cognitive-behavioral group treatment for chronic low back pain. J Consult Clin Psychol 1988;56:261–6.
31. Bossard AE, Guirimand F, Fletcher D, Gaude-Joindreau V, Chauvin M, Bouhassira D. Interaction of a combination of morphine and ketamine on the nociceptive flexion reflex in human volunteers. Pain 2002;98:47–57.
32. Le Bars D, Willer JC, de Broucker T. Morphine blocks descending pain inhibitory controls in humans. Pain 1992;48: 13–20.
33. Sandrini G, Gli Uberti EC, Salvadori S, Margutti A, Trasforini G, Tomatis R, et al. Dermorphin inhibits spinal nociceptive flexion reflex in humans. Brain Res 1986;371:364–7.

## 6. CONSIDERAÇÕES GERAIS

Tendo em vista a natureza preliminar deste estudo piloto, seus resultados positivos iniciais merecem replicação em projetos com maior número de participantes. A principal aplicação clínica dos resultados deste trabalho é o conhecimento de que, através de técnicas não-farmacológicas, o *déficit* nociceptivo pode, de fato, ser melhorado em pacientes com FM.

O conhecimento embasado das associações psicobiológicas na fibromialgia poderia trazer avanços no conhecimento da sua fisiopatologia que tornariam mais eficazes e duradouras eventuais medidas preventivas e terapêuticas. Além disso, também poderiam ser identificados biomarcadores com melhor aplicabilidade clínica, auxiliando no diagnóstico, prognóstico e acompanhamento destes pacientes. Por fim, a proposta de categorização dos pacientes portadores de fibromialgia em subgrupos, de acordo com determinadas características clínicas e fisiopatológicas predominantes, poderia ganhar importante contribuição a partir destes estudos, permitindo o uso de medidas de tratamento mais individualizadas e bem sucedidas.

# 7. ANEXOS

## **Anexo I: Critérios de classificação para fibromialgia do *American College of Rheumatology*, 1990** (120)

Segundo estes critérios, um indivíduo pode ser classificado como tendo fibromialgia se as duas condições abaixo estiverem presentes.

1 - Dor difusa crônica

Definição: dor, para ser considerada como difusa, deve estar presente no lado esquerdo e direito do corpo, bem como acima e abaixo da cintura. Além disso, dor axial (coluna ou tórax anterior) deve estar presente. A história de dor difusa deve estar presente há pelo menos 3 meses, e outras condições clínicas não excluem o diagnóstico de fibromialgia.

2 - Dor em pelo menos 11 de 18 pontos dolorosos, à palpação digital (Figura 3)

Definição: dor (e não dolorimento), à palpação digital com força aproximada de 4Kg, em pelo menos 11 de 18 pontos dolorosos mencionados abaixo:

- Occipital: bilateral, na inserção dos músculos suboccipitais.
- Cervical baixo: bilateral, nos aspectos anteriores dos espaços intertransversos de C5 a C7.
- Trapézio: bilateral, no ponto médio da sua borda superior.
- Supraespinhoso: bilateral, na sua origem, acima da espinha da escápula, perto da sua borda medial.
- Segunda costela: bilateral, na segunda articulação costocondral, imediatamente lateral à articulação, na borda superior da costela.

- Epicôndilo lateral: bilateral, 2 cm distal dos epicôndilos.
- Glúteo: bilateral, nos quadrantes superiores externos das nádegas, na borda anterior dos músculos.
- Trocanter maior: bilateral, posterior à proeminência trocantérica.
- Joelho: bilateral, no coxim de gordura medial proximal à linha articular.

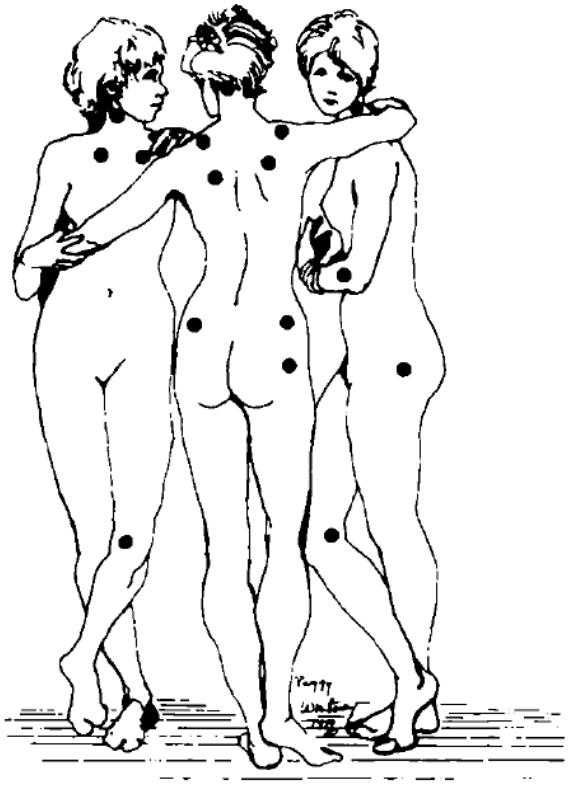

**Figura 3**: Pontos dolorosos da fibromialgia. Adaptado de Wolfe F *et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia*. Arthritis & Rheumatism. 1990 Feb;33(2):160-72.

**Anexo II: Critérios diagnósticos modificados para fibromialgia do *American College of Rheumatology*, 2011 (121)**

Um paciente satisfaz estes critérios se as três condições subsequentes forem alcançadas: (1) índice de dor difusa (IDD) ≥ 7 e escore de gravidade de sintomas (EGS) ≥ 5 ou IDD 3-6 e EGS ≥ 9; (2) sintomas presentes em níveis semelhantes há pelo menos 3 meses; (3) o paciente não tem outra condição que explicaria de outra forma a dor.

**Índice de dor difusa** (IDD, 0-19): número de áreas em que o paciente apresentou dor na última semana.

| | | | |
|---|---|---|---|
| Cintura escapular esquerda | Quadril esquerdo | Mandíbula esquerda | Coluna dorsal |
| Cintura escapular direita | Quadril direito | Mandíbula direita | Coluna lombar |
| Braço esquerdo | Coxa esquerda | Tórax | Pescoço |
| Braço direito | Coxa direita | Abdome | |
| Antebraço/mão esquerdos | Perna/pé esquerdos | | |
| Antebraço/mão direitos | Perna/pé direitos | | |

**Escore de gravidade de sintomas** (EGS, 0-12): soma das gravidades* (na última semana) de fadiga, despertar de sono não-restaurador e sintomas cognitivos com o número dos seguintes sintomas presentes (no últimos 6 meses) – cefaléias, dor ou cólica em baixo ventre e depressão.

*0=Sem problema; 1=Leve (problemas geralmente brandos ou intermitentes); 2=Moderado (problemas consideráveis, presentes com frequência e/ou em níveis moderados); 3=Grave (problemas predominantes, contínuos, perturbadores da vida).

## Anexo III: Termo de consentimento livre e esclarecido (versão original).

A Pilot Study on the Use of Nociceptive Flexion Reflex for Fibromyalgia

You are invited to take part in a 12-week study entitled, "A Pilot Study on the Use of Nociceptive Flexion Reflex for Fibromyalgia". If you agree to participate, you will be one of the 30 female volunteers with fibromyalgia who will take part in this study.

**STUDY PURPOSE:**

We are doing this study to better understand the role of the central nervous system in processing painful stimuli in patients with fibromyalgia. Specifically, we would like to know whether the central nervous system processing of painful stimuli changes *with time and with talk therapy*. In addition, we are investigating how changes in your fibromyalgia symptoms may affect certain markers or proteins in your blood.

This informed consent will explain who is qualified to participate, what you will be asked to do while in the study and how study data will be collected. Once you have reviewed the informed consent and HIPAA authorization form, you will be given the opportunity to ask questions regarding the study and the procedures. Then, if you are willing to participate you will be asked to sign this document. You will be given a copy of the documents you sign today.

**WHO IS QUALIFIED TO PARTICPATE?**

The inclusion criteria are as follows:

1. Female volunteers who have been diagnosed with fibromyalgia by a rheumatologist.
2. Overall body pain average score $\geq 4$
3. Age range: 18 to 65 years old
4. For volunteers taking fibromyalgia-related medications such as cyclobenzaprine, tramadol, gabapentin, pregabalin, amitriptyline, nortriptyline, trazodone, sertraline, fluoxetine, paxil, remeron, venlafaxine and duloxetine must be on stable doses of each medication (at least 4 weeks).
5. Willingness for record all medications taken during a 48-hour time period prior to each of the three testing phases.
6. Willingness to limit changes in your list of medications that are commonly prescribed for pain, sleep, anxiety, and depression (e.g., muscle relaxant, pain medication, antidepressant, cymbalta, lyrica, gabapentin, etc.) during the 12-week study period unless medically necessary.
7. Willingness to abstain (not take) medications classified as NSAIDS for at least 48-hours prior to each of the three testing session. The following medications are classified as NSAIDs: Celebrex, Naproxen, Aleve, Anaprox, Ibuprofen, Motrin, Advil, Voltaren, Cataflam, Arthrotec, Diclofenac,Etodolac, Lodine, Lodine XL, Daypro, Oxaprozin, Relafen, Nabumetone, Ketoprofen, Orudis, Oruvail, Piroxicam, Feldene, Sulindac, Clinoril, Mobic, Meloxicam, Salsalate, Amigesic, Disalcid, Trilisate choline magnesium, Trisalicylate, Indocin, and Dolobid.

The exclusion criteria are as follows:

1. Volunteers who have long-standing history of diabetes (> 2 years), or have been diagnosed with any type of peripheral neuropathy.
2. Have a prior history of myocardial infarction (heart attack) or unstable angina or other heart arrhythmias.
3. Have been diagnosed with multiple sclerosis or any other demyelinating disorder.
4. Have planned to undergo an elective surgery over the next 12 weeks.
5. Have other major rheumatic conditions (i.e. rheumatoid arthritis, systemic lupus erythematosus, scleroderma and other connective tissue disease)
6. Are currently pregnant or actively trying to become pregnant
7. Unwillingness to comply with all items listed in the inclusion criteria

**WHAT HAPPENS AFTER I QUALIFY?**

You will be asked to visit the Fibromyalgia Clinical Research Center on 3 different occasions: baseline (today's visit), week 6, and week 12.

During today's visit, you will be randomly assigned to one of two groups. Similar to flipping a coin, you have a 50% chance of being assigned to either one of two groups: a) telephone-based educational instruction group or b) usual care group. Subjects who are randomly assigned to educational instruction group will receive one phone call per week for the first six weeks of the study. During the phone conversation, you will receive instructions in managing your pain. If you are assigned to the educational instruction group, you must agree to allow us to audiotape the telephone conversation. Audio-taping the telephone conversations will help us give you the highest quality of instruction. On the other hand, subjects assigned to the usual care group will receive no telephone calls from the research team.

During <u>each</u> visit you will be asked to do the following:

1. Complete a comprehensive questionnaire (computer-based or the traditional paper and pen format) in regard to how fibromyalgia affects your daily living.

   **Risks:** You may feel uncomfortable or care not to answer a particular question.
   **To minimize these risks**, you can tell the researcher that you feel uncomfortable or do not wish to answer the question.

2. Provide a 10 ml blood sample prior to each of the three test The purpose of these blood tests are to examine changes in certain blood markers in relation to your changes in your symptoms

   **Risks:**
   The physical risks associated with participation in this study are with the blood draw. The process of drawing blood may cause bleeding, bruising, pain, lightheadedness, and some minor swelling around the area of the needle stick. Occasionally an infection or bleeding may develop where the needle was placed in the vein.
   **To minimize these risks**, the blood specimen will be obtained by experienced technicians.

3. Undergo nociceptive flexion reflex (NFR) testing.
   This test examines how your body responds to painful stimuli (reflex). To begin each testing session, electrodes used to measure the reflex will be attached to your left leg. To measure the reflex, we will administer a series of electrical stimuli to the ankle of your left foot. After each stimulus you will be asked to rate the stimulus intensity using a scale with anchors of 0 (no sensation), 50 (pain threshold), and 100 (maximum tolerable). This

procedure is used to determine the intensity of stimulus required to elicit a nociceptive flexion reflex response from your left hamstring muscle. This reflex is so small that you may not even notice any activity in your leg muscles. The intensity of electrical stimuli will be increased slowly until a reflex response is shown, but the intensity will NEVER exceed that which you rate as a "100" (maximum tolerable). At the higher intensities, the electrical stimulus is described by others as feeling like a "brief pinprick" or "carpet shock".
We will use the same procedure to assess your pain tolerance threshold for electrical stimulation to your ankle. Stimulus intensity will be increased slowly and you will be asked to rate each stimulus on the 0-100 scale. The procedure will end as soon as you provide a stimulus intensity rating of "100" (maximum tolerable).

**Risks:**
The nociceptive flexion reflex procedure is likely to elicit temporary discomfort, increases in heart rate and blood pressure as well as sensations of discomfort or pain. Further, preparation of the skin required to apply electrodes may be mildly irritating or uncomfortable, and may leave behind some redness of the skin that could require a few days to heal.
**To minimize these risks,** only well trained technicians will conduct this test. It is important to note that this test is similar to an EMG (electromyogram) study – a test commonly done in routine medical care.

**Risks:**
If you participation in this study, loss of confidentiality of personal and medical information is the possible.
**To minimize this potential risk**, every effort will be made to keep your personal information confidential. In order to protect your confidentiality we will ensure that: Any file containing your personal information will be kept in a private area of our offices. The files will be made secure and will be maintained and accessed only by authorized staff. Your personal and medical information will not be released to any insurance company, potential employer, government agent or agency, family member, or friend. However, the information may be disclosed if required by law, to federal regulatory agencies such as the Food and Drug Administration, and to the Institutional Review Boards and their designees. Published results from research on your sample will not identify you.

**BENEFITS IN TAKING PART IN THE STUDY:**

**There is no direct benefit to taking part in this study.** However, the information we learn from data collected in this study may provide a better understanding of the cause of fibromyalgia and management of this illness.

**ALTERNATIVES TO TAKING PART IN THE STUDY:**

You have the option of not participating in the study. Your decision not to participate will not affect your health care or your doctor's interest in you. If you no longer wish to participate at any time during the study period, you may contact the project coordinator, Janna Hilligoss at 317-274-1755.

**CONFIDENTIALITY:**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published and databases in which results may be stored.

If you are randomly assigned to the telephone-based educational instruction group: Only 2 members of the research team (one fellow investigator and one research nurse) will have access to the audio-taped telephone conversation. Audio-taping the telephone conversation will help train our research nurse to provide the highest quality of encouragement or educational instruction. The audio-tape will be permanently deleted one month from the time it is recorded.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the IUPUI/Clarian Institutional Review Board or its designees, (as allowed by law) state or federal agencies (specifically the Office for Human Research Protections (OHRP) and the National Institutes of Health (NIH) may need to access your medical and/or research records.

**COSTS:**

There are no costs associated with participation in the study.

**PAYMENT**:

To cover for gas expenditure and your time off from work, you will be reimbursed upon completion of each phase of the study. The schedule is as follows:

Today, if you qualify to enter the study, and participate in the baseline data collection as described above you will receive $50. If you do not qualify, you will receive $10.00.

For week 6 visit, you will receive $75.
For week 12 visit: $100
Parking space is free for the required 3 visits.
Payment may be received per session or upon completion of the study.

**COMPENSATION FOR INJURY:**

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled.

**CONTACTS FOR QUESTIONS OR PROBLEMS:**

For questions or concerns about the study or a research–related injury, contact the principal researcher Dr. Dennis C. Ang at 317-274-4225. If you cannot reach the researcher during regular business hours (i.e. 8:00AM-5:00 PM), please call the IUPUI/Clarian Research Compliance Administration office as 317-278-3458 or 1-800-696-2949. After business hours, please call the rheumatology fellow on-call at 317-274-5000.
In the event of an emergency, you may contact Dr. Dennis C. Ang at 317-274-5000

For questions about your rights as a research participant or to discuss problems, complaints or concerns about a research study, or to obtain information or to offer input, contact the IUPUI/Clarian Research Compliance Administration office at 317-278-3458 or 1-800-696-2949.

**VOLUNTARY NATURE OF STUDY:**

Taking part in this study is voluntary. You may choose not to take part or may leave at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Indiana University Medical Center or your treating rheumatologist.

**SUBJECT'S CONSENT:**

In consideration of all the above, I give my consent to participate in this research study. I will be given a copy or this informed consent to keep for my records.

SUBJECT'S SIGNATURE: _____ Date: _____

Contact telephone number: _____

SIGNATURE OF PERSON OBTAINING CONSENT: _____Date: _____

**Anexo IV: Questionários de avaliação (versão original).**

**BRIEF PAIN INVENTORY (BPI)**

**The questions below would relate to your <u>overall body pain</u>.**

1. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last week.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Pain as bad as you can imagine |

2. Please rate your pain by circling the one number that best describes your pain at its **least** in the last week.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Pain as bad as you can imagine |

3. Please rate your pain by circling the one number that best describes your pain on the **average** in the last week.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Pain as bad as you can imagine |

4. Please rate your pain by circling the one number that tells how much pain you have **right now**.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No Pain | | | | | | | | | | Pain as bad as you can imagine |

5. In the last week, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

| 0% | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
|---|---|---|---|---|---|---|---|---|---|---|
| No Relief | | | | | | | | | | Complete Relief |

6. If you take pain medication, how many hours does it take before the pain returns?
   1. Pain medication doesn't help at all
   2. One hour
   3. Two hours
   4. Three hours
   5. Four hours
   6. Five to twelve hours
   7. More than twelve hours
   8. I do not take pain medication
7. Circle the one number that describes how, during the **past week**, pain has interfered with your:

A. General Activity

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does Not Interfere | | | | | | | | | | Completely Interferes |

B. Mood

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does Not Interfere | | | | | | | | | | Completely Interferes |

C. Walking Ability

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does Not Interfere | | | | | | | | | Completely Interferes | |

D. Normal Work (includes both work outside the and housework)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Does Not | | | | | | | | | | Completely |

Interfere Interferes

E. Relations With Other People

0 1 2 3 4 5 6 7 8 9 10

Does Not Interfere Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10

Does Not Interfere Completely Interferes

G. Enjoyment Of Life

0 1 2 3 4 5 6 7 8 9 10

Does Not Interfere Completely Interferes

## FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

**Directions:** For questions 1 through 11, please choose the number that best describes how you did overall for the **PAST WEEK**. If you don't normally do something that is asked, cross the question out.

| | Always | Most | Occasionally | Never |
|---|---|---|---|---|
| **Were you able to:** | | | | |
| 1. Do shopping? | 0 | 1 | 2 | 3 |
| 2. Do laundry with a washer and dryer? | 0 | 1 | 2 | 3 |
| 3. Prepare meals? | 0 | 1 | 2 | 3 |
| 4. Washes dishes/cooking utensils by han. | 0 | 1 | 2 | 3 |
| 5. Vacuum a rug? | 0 | 1 | 2 | 3 |
| 6. Make beds? | 0 | 1 | 2 | 3 |
| 7. Walk several blocks? | 0 | 1 | 2 | 3 |
| 8. Visit friends or relatives? | 0 | 1 | 2 | 3 |
| 9. Do yard work? | 0 | 1 | 2 | 3 |
| 10. Drive a car? | 0 | 1 | 2 | 3 |
| 11. Climb stairs? | 0 | 1 | 2 | 3 |

12. Of the 7 days in the past week, how many days did you feel good?

0 1 2 3 4 5 6 7

13. How many days last week did you miss work, including housework, because of fibromyalgia?

0 1 2 3 4 5 6 7

**Directions**: For item number 14 to 20, mark the point on the line that best indicates how you felt overall for the **PAST WEEK.**

14. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework?

●___|___|___|___|___|___|___|___|___|___|___●

No problem with work Great difficulty with work

15. How bad has your pain been?

●___|___|___|___|___|___|___|___|___|___|___●

No pain Very severe pain

16. How tired have you been?

●___|___|___|___|___|___|___|___|___|___|___●

No tiredness Very tired

17. How have you felt when you get up in the morning?

●___|___|___|___|___|___|___|___|___|___|___●

Awoke well rested Awoke very tired

18. How bad has your stiffness been?

●___| ___|___| ___|___| ___| ___| ___| ___|___●

No stiffness Very stiff

19. How nervous or anxious have you felt?

●___| ___|___| ___|___| ___| ___| ___| ___|___●

Not anxious Very anxious

20. How depressed or blue have you felt?

●___| ___|___| ___|___| ___| ___| ___| ___|___●

Not depressed Very depressed

**Patient Health Questionnaire-8 (PHQ-8)**

| Over the **LAST 2 WEEKS**, how often have you been bothered by any of the following problems? | **Not at all** | **Several days** | **More than half the days** | **Nearly every day** |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things..... | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless..... | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much..... | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy..... | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating..... | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down…… | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television…….. | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving .around a lot more than usual..... | 0 | 1 | 2 | 3 |

**SF-36 Vitality**

These questions are about how you feel and how things have been with you **during the past month**. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the **past month**…

| | All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|---|
| 1. Did you feel full of pep? | | | | | | |
| 2. Did you have a lot of energy? | | | | | | |
| 3. Did you feel worn out? | | | | | | |
| 4. Did you feel tired? | | | | | | |

**Sleep-related Questions**

1. In the **last 2 weeks**, how would you rate the severity of your sleeping problem?

| | None | Mild | Moderate | Severe | Very |
|---|---|---|---|---|---|
| Difficulty falling asleep: | 0 | 1 | 2 | 3 | 4 |

Difficulty staying asleep: 0 1 2 3 4
Problem waking up too early: 0 1 2 3 4

2. How SATISFIED/dissatisfied are you with your current sleep pattern?

| Very Satisfied | | | | Very Dissatisfied |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

**3.** To what extent do you consider your sleep problem to INTERFERE with your daily functioning (example: daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)

| Not at all Interfering | A little | Somewhat | Much | Very much Interfering |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

4. How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?

| Not at all Noticeable | Barely | Somewhat | Much | Very much Noticeable |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

**5.** How WORRIED/distressed are you about your current sleep problem?

| Not at all | A little | Somewhat | Much | Very much |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

**MULTIPLE ABILITY SELF-REPORT QUESTIONNAIRE (MASQ)**

**Instructions**: *Please rate your ability to perform the activities below according to the following five-point scale. Please indicate 1=never, 2=rarely, 3=sometimes, 4=usually, or 5=always.*

| | **Never** | **Rarely** | **Sometimes** | **Usually** | **Always** |
|---|---|---|---|---|---|
| 1. When talking, I have difficulty conveying precisely what I mean. | | | | | |
| 2. I can follow telephone conversations. | | | | | |
| 3. I find myself searching for the right word to express my thoughts. | | | | | |
| 4. My speech is slow or hesitant. | | | | | |
| 5. I find myself calling a familiar object by the wrong name. | | | | | |
| 6. I find it easy to make sense out of what people say to me. | | | | | |
| 7. People seem to be speaking too fast. | | | | | |
| 8. It is easy for me to read and follow a newspaper story. | | | | | |
| 9. I can easily fit the pieces of a jig-saw puzzle together. | | | | | |
| 10. I am able to follow the | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| visual diagrams that are included in “easy to assemble” products. | | | | | |
| 11. I have difficulty locating a friend in a crowd of people. | | | | | |
| 12. I have difficulty estimating distances (for example; from my house to a house of a relative). | | | | | |
| 13. I get lost when traveling around. | | | | | |
| 14. It is hard for me to read a map to find a new place. | | | | | |
| 15. I forget to mention important issues during conversations. | | | | | |
| 16. I forget important things I was told just a few days ago. | | | | | |
| 17. I am able to recall the details of the evening news report several hours later. | | | | | |
| 18. I forget important events which occurred over the past month. | | | | | |
| 19. I forget the important portions of gossip I have heard. | | | | | |
| 20. I forget to give phone call messages. | | | | | |
| 21. I have to hear or read something several times before I can recall it without difficulty. | | | | | |
| 22. I can recall the names of people who were famous when I was growing up. | | | | | |
| 23. After putting something away for safekeeping, I am able to recall its location. | | | | | |
| 24. When I first go to a new restaurant, I can easily find my way back to the table when I get up. | | | | | |
| 25. I have difficulty finding | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| stores in a mall even if I have been there before. | | | | | |
| 26. I can easily locate an object that I know is in my closet. | | | | | |
| 27. I have difficulty remembering the faces of the people I have recently met. | | | | | |
| 28. After the first visit to a new place, I can find my way around with little difficulty (*e.g.* restaurant, department store) | | | | | |
| 29. I remember the pictures that accompany magazine or newspaper articles I have recently read. | | | | | |
| 30. I can easily pick out my coat from among others on a coat rack. | | | | | |
| 31. I can do simple calculations in my head quickly. | | | | | |
| 32. I ask people to repeat themselves because my mind wanders during conversations. | | | | | |
| 33. I am alert to things going on around me. | | | | | |
| 34. I have difficulty sitting still to watch my favorite TV programs. | | | | | |
| 35. I am easily distracted from my work by things going on around me. | | | | | |
| 36. I can keep my mind on more than one thing at a time. | | | | | |
| 37. I can focus my attention on a task for more than a few minutes at a time. | | | | | |
| 38. I find it difficult to keep my train of thought going during a short interruption. | | | | | |

**PAIN RELATED THOUGHTS AND FEELINGS**

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be

associated with pain. Using following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

**0 = not at all**
**1 = to a slight degree**
**2 = to a moderate degree**
**3 = to a great degree**
**4 = all the time**

**When I'm in pain……**

**1.** I worry all the time about whether the pain will end. ..... 0 1 2 3 4
**2.** I feel I can't go on. ..... 0 1 2 3 4
**3.** It's terrible and I think it's never going to get any better. ..... 0 1 2 3 4
**4.** It's awful and I feel that it overwhelms me. ..... 0 1 2 3 4
**5.** I feel I can't stand it any more. ..... 0 1 2 3 4
**6.** I become afraid that the pain may get worse. ..... 0 1 2 3 4
**7.** I keep thinking of other painful experiences. ..... 0 1 2 3 4
**8.** I anxiously want the pain to go away. ..... 0 1 2 3 4
**9.** I can't seem to keep it out of my mind. ..... 0 1 2 3 4
**10.** I keep thinking about how much it hurts. ..... 0 1 2 3 4
**11.** I keep thinking about how badly I want the pain to stop. ..... 0 1 2 3 4
**12.** There is nothing I can do to reduce the intensity of the pain. ... 0 1 2 3 4
**13.** I wonder whether something serious may happen. ..... 0 1 2 3 4

**AES**

Directions: A number of statements which people have used to describe themselves when they feel angry or furious are given below. Read each statement and then circle the appropriate number to indicate how often you feel or act in the manner described when angry or furious. There are no right or wrong answers. Do not spend too much time on any one statement. For each item, circle the number which seems to best describe how you generally act or feel.

| | Almost Never | Sometimes | Often | Almost Always |
|---|---|---|---|---|
| 1. I control my temper. | 1 | 2 | 3 | 4 |
| 2. I express my anger. | 1 | 2 | 3 | 4 |
| 3. I keep things in. | 1 | 2 | 3 | 4 |
| 4. I make threats I don't mean to carry out. | 1 | 2 | 3 | 4 |
| 5. I pout or sulk. | 1 | 2 | 3 | 4 |
| 6. I withdrew from people. | 1 | 2 | 3 | 4 |
| 7. I make sarcastic remarks to others. | 1 | 2 | 3 | 4 |
| 8. I keep my cool. | 1 | 2 | 3 | 4 |
| 9. I do things like slamming doors. | 1 | 2 | 3 | 4 |
| 10. I boil inside, but I don't show it. | 1 | 2 | 3 | 4 |
| 11. I argue with others. | 1 | 2 | 3 | 4 |
| 12. I tend to harbor grudges that I don't tell anyone about. | 1 | 2 | 3 | 4 |
| 13. I strike out at whatever infuriates me. | 1 | 2 | 3 | 4 |
| 14. I am secretly critical of others. | 1 | 2 | 3 | 4 |
| 15. I am angrier than I am willing to admit. | 1 | 2 | 3 | 4 |
| 16. I calm down faster than most other people do. | 1 | 2 | 3 | 4 |
| 17. I say nasty things. | 1 | 2 | 3 | 4 |

| | | | | |
|---|---|---|---|---|
| 18. I am irritated a great deal more than people are aware of. | 1 | 2 | 3 | 4 |
| 19. I lose my temper. | 1 | 2 | 3 | 4 |
| 20. If someone annoys me, I am apt to tell him or her how I feel. | 1 | 2 | 3 | 4 |

**Treatment Survey at BASELINE**

1. When did your fibromyalgia pain first start? Year _____ (estimate)
2. Have you ever been seen in a pain clinic?
   ____ Never (0) ____ Yes, but not now (1) ____ Yes, currently (2)
3. Have you ever been seen (treated) by a counselor, psychiatrist, or psychologist?
   ____ Never (0) ____ Yes, but not now (1) ____ Yes, currently (2)
4. Have you ever had any of the following treatments for pain?
   a. Physical therapy
      ____ Never (0)
      ____ Yes, but not now (1)
      ____ Yes, currently (2)
   b. Seen a specialist such as a … [check all that apply]
      i) ____ neurologist
      ii) ____ orthopedist
      iii) ____ rheumatologist
      iv) ____ other specialist doctor [List _____]
   c. Seen a chiropractor
      ____ Never (0)
      ____ Yes, but not now (1)
      ____ Yes, currently (2)
   d. Acupuncture
      ____ Never (0)
      ____ Yes, but not now (1)
      ____ Yes, currently (2)
   e. Massage
      ____ Never (0)
      ____ Yes, but not now (1)
      ____ Yes, currently (2)
   f. Seen any other practitioners or had other treatments (besides medicines) for pain?
      i) Treatment 1 [List _____]
         ____ Never (0)
         ____ Yes, but not now (1
         ____ Yes, currently (2)
      ii) Treatment 2 [List _____]
         ____ Never (0)
         ____ Yes, but not now (1)
         ____ Yes, currently (2)

**DEMOGRAPHICS (for BASELINE assessment ONLY)**

Date of birth_____ (mm, dd, yy) Age at study enrollment ____

What is the highest grade or level of schooling that you completed?

1. 8TH Grade or less
2. Some high school
3. High School or GED
4. Technical trade or business school
5. 2-year college degree or some college

6. 4-year college degree
7. Post-graduate degree (*e.g.*, masters or doctorate)
99. Don't know or refused to answer

What race or ethnic group do you consider yourself to be? ____
(Choose one?)

1. White (Caucasian)
2. Black or African American
3. Hispanic, Spanish or Latino
4. American Indian or Alaska Native
5. Asian
6. Other Specify _____ (includes space for write-ins)
99. Don't know or refused to answer

Gender

1. Male
2. Female

Are you married, divorced, widowed, separated, never married, or a member of an unmarried couple?

1. Married
2. Divorced
3. Widowed
4. Separated
5. Never married
6. A member of an unmarried couple
99. Don't know or refused to answer

Which of the following best describes your current employment (work) situation? Are you currently (Choose one most reflective):

1. Employed for wages
2. Self-employed
3. Out of work for more than 1 year
4. Out of work for less than 1 year
5. Homemaker
6. Student
7. Retired
8. Unable to work (for health or disability reasons)
98. Other
99. Don't know or refused to answer

When you consider your household income from all sources, (today), would you say that you are comfortable, Have just enough to makes ends meet, or Do NOT have enough to make ends meet?

1. Comfortable
2. Just enough to make ends meet
3. NOT enough to make ends meet
99. Don't know or refused to answer

**CONTACT INFORMATION**

To stay in contact with you during the course of this project, it will be very important that we always have a current telephone number where we can reach you.

**1) *What is your current telephone number? ( _ _ _ ) _ _ _ - _ _ _ _***

2) What is the best time to reach you? (RECORD ALL THAT APPLY)

WEEKDAYS 1
WEEKENDS 2

AM 3
PM 4

3) Sometimes people move or change their telephone number during the course of a project. Do you expect to make any such changes over the coming year?

YES 1
NO 2
DK 8
REF 9

4) What is your address?

STREET_____
CITY _____
ZIP_____

If you do make changes, please call the project manager, _____at _____and mail this postcard with your new forwarding information to the survey research group [GIVE A POSTCARD], to make sure she has your new telephone number.

Since we will be contacting you in the future, would you mind giving us a contact person, in the event you move? This would be someone who lives outside your home. (NOTE NAME, RELATIONSHIP, ADDRESS AND PHONE OF CONTACT PERSON(S))

FULL NAME_____
RELATIONSHIP_____
STREET_____
CITY _____
ZIP_____
TELEPHONE NUMBER_____

**ADDITIONAL ITEMS FOR WEEK 6 AND WEEK 12**

**GRC. Overall, since starting the study, would you say your overall body pain is:**

1 WORSE
2 ABOUT THE SAME
3 BETTER

[PATIENTS WHO STATE THEY ARE BETTER ARE THEN ASKED:]

How much better is your overall body pain? Is it:

1 A LITTLE BETTER
2 SOMEWHAT BETTER
3 MODERATELY BETTER
4 A LOT BETTER
5 COMPLETELY BETTER (Pain is Gone)

Below is the list of fibromyalgia medications that you were on the last time you completed the survey.

| Name of medication | Dose | Frequency (Average per day) |
|---|---|---|
| 1. | | |
| 2. | | |
| 3. | | |
| 4. | | |
| 5. | | |
| 6. | | |

5. Is there any medication listed that you are NOT taking anymore?
   ____ Yes [which drug? _____]
   ____ No
6. Has there been a change in the dosage of any of the medications listed above?
   ____ Yes ____ No

7. Has there been a change in the average frequency of intake (per day) of any of the medications listed above?
   ____ Yes ____ No
8. Are you taking any new medication for fibromyalgia?
   ____ Yes ____ No

**Direction:** If you answer '**yes**' to anyone of questions 7 to 9, kindly write the changes made (or any new medication) in the space provided below.
Under the **dose column**, write the strength or the number of milligram. Under the **frequency column,** write the **AVERAGE** number of pills you take in a day.
[*Instruction to the Database Programmer*: Subject may or may not need to complete the DOSE column]

| Name of medication | Dose | Frequency (Average per day) |
|---|---|---|
| 1. | | |
| 2. | | |
| 3. | | |
| 4. | | |
| 5. | | |
| 6. | | |

**We would like to ask you some questions about any special treatments that you may have had since the last time you completed the survey.**

1. Have you been seen in a pain clinic?
   ____ No (0)
   ____ Yes (1)
2. Have you had any of the following treatments for body pain?
   a. Physical therapy
      ____ No (0)
      ____ Yes (1)
   b. Seen a specialist such as a … [check all that apply]
      v) ____ neurologist
      vi) ____ orthopedist
      vii) ____ rheumatologist
      viii) ____ other specialist doctor [List _____]
   c. Seen a chiropractor
      ____ No (0)
      ____ Yes (1)
   d. Acupuncture
      ____ No (0)
      ____ Yes (1)
   e. Massage
      ____ No (0)
      ____ Yes (1)
   f. Seen any other practitioners or had other treatments (besides medicines) for pain?
      ____ No (0)
      ____ Yes (1) → If "Yes", complete following:
      i) Treatment 1 [List _____]
      ii) Treatment 2 [List _____]
3. Have you been seen (treated) by a counselor, psychiatrist, or psychologist?
   ____ No (0)
   ____ Yes (1)

**Anexo V: Protocolo de estudo (versão original).**

**Definitions and protocols**

**Four NFR threshold definitions:**

1. NFR threshold returned by the software (mA) at the end of the test calculated as the average of the four following values: (1) the level of stimulation at which the first reflex of the second "group" of reflexes is detected, (2) the first level of stimulation at which the reflex disappears (no reflex) afterwards, (3) the level of stimulation at which the first reflex of the third "group" of reflexes is detected, (2) the first level of stimulation at which the reflex disappears (no reflex) afterwards (the final row of the test).
2. In those subjects with no returned threshold, but with >= 1 reflexes detected, get the average of the stimulus intensities (mA) that resulted in a reflex.
3. Area Under the Curve (AUC): plot the # of trials (x-axis) against the NFR amplitude (y-axis). Start plotting with the first trial and end with the trial where the first reflex is observed (up slope).
4. The intensity (mA) of the stimulus that produced the FIRST reflex (up slope).

**Three Summation definitions:**

1. Classic NFR summation: at least 2 reflex among the last three stimuli and no reflex in the first two.
2. Pain 'self-report' summation: an increment of 3 or more in the difference of the pain rating between the highest value of the last three stimuli and the lowest of the first two.
3. Amplitude summation: an increment of 1 Average Baseline Standard Deviation or more in the NFR value (uV) between the highest value of the last three stimuli and the lowest of the first two

**NFR Threshold Protocol:**

1) Maximum level of stimulation set at 60 mA = August 10, 2008
2) Endpoints:
   - 2.1) 3 "disappearances" of reflexes, expressed by 3 different "-1" values in column "Rev"
   - 2.2) self-report pain score >=95
   - 2.3) patient refuses to proceed with the study (the examiner may score 100)

**NFR summation Protocol:**

1) Maximum level of stimulation set at 40 mA= July 26, 2008
2) Protocol change = August 28, 2008
   - 2.1) Start at 1 mA and increment 4 mA per iteration until summation is observed (or the upper limit of 40 mA or pain rating of 95 or higher) is reached.
   - 2.2) If summation is observed, drop the stimulation level 10 mA and elicit summation again, this time incrementing 2 mA/iteration.
   - 2.3) Then drop 5 mA and increment 1 mA/iteration until summation is observed a third time.
3) Endpoints:
   - 3.1) Classic summation detected
   - 3.2) self-report pain score >=95
   - 3.3) patient refuses to proceed with the study (the examiner may score 100 for each of the 5 stimuli)

**Baseline EMG activity increment in the summation phase is present when:**

the difference between the last and the first stimuli baseline EMG activity [on column "Base (uV)"] is equal to or greater than 1 Average Baseline Standard Deviation [Avg BaseSD (uV)]

| Measures and Instruments | | | |
|---|---|---|---|
| **INDIVIDUAL VARIABLES** | **BASELINE** | **WEEK 6** | **WEEK 12** |
| **OBJECTIVE TEST VARIABLES** | | | |
| Protocol | X | X | X |
| ***NFR threshold phase*** | | | |
| NFR threshold | X | X | X |
| Mean Pain Rating at NFR Threshold | X | X | X |
| Number of reflexes achieved | X | X | X |
| Intensity of the first reflex | X | X | X |
| Area under the NFR curve | X | X | X |
| Mean baseline activity before the first reflex | X | X | X |
| Mean baseline activity after the first reflex | X | X | X |
| Endpoint | X | X | X |
| ***Summation phase*** | | | |
| Number of classic summations detected | X | X | X |
| Classic summation threshold | X | X | X |
| First classic summation intensity | X | X | X |
| First block with classic summation | X | X | X |
| Number of amplitude summations detected | X | X | X |
| Amplitude summation threshold | X | X | X |
| First amplitude summation intensity | X | X | X |
| First block with amplitude summation | X | X | X |
| Number of pain summations detected | X | X | X |
| Pain summation threshold | X | X | X |
| First pain summation intensity | X | X | X |
| First block with pain summation | X | X | X |
| Number of summation baseline activity increment detected | X | X | X |
| Summation baseline activity increment | X | X | X |
| First summation baseline activity increment detected | X | X | X |

| | | | |
|---|---|---|---|
| First block with baseline activity increment | X | X | X |
| Endpoint | X | X | X |
| **SELF-REPORT VARIABLES** | | | |
| Fibromyalgia impact questionnaire (FIQ) | X | X | X |
| Brief pain inventory (BPI) | X | X | X |
| SF-36 vitality | X | X | X |
| Sleep-related questionnaire (Insomnia severity index – ISI) | X | X | X |
| Multiple ability self-report questionnaire (MASQ) | X | X | X |
| Pain-related thoughts and feelings (Pain catastrophizing scale - PCS) | X | X | X |
| Patient health questionnaire-8 (PHQ-8) | X | X | X |
| Anger Expression Scale (AES) | X | X | X |
| Anxiety questionnaire | X | X | X |
| **CLINICAL VARIABLES** | | | |
| Height | X | X | X |
| Weight | X | X | X |
| Blood pressure | X | X | X |
| Year of pain onset | X | | |
| **HEALTH CARE UTILIZATION VARIABLES** | | | |
| Pain clinic | X | X | X |
| Counselor, psychologist, psychiatrist | X | X | X |
| Other treatments | X | X | X |
| Pain level follow-up | | X | X |
| Medication discontinued | | X | X |
| Medication dose change | | X | X |
| Medication frequency change | | X | X |
| New medication | | X | X |
| **DEMOGRAPHICAL VARIABLES** | | | |
| Date of birth | X | | |
| Age at study enrollment | X | | |

| | | | |
|---|---|---|---|
| Educational level | X | | |
| Race | X | | |
| Gender | X | | |
| Marital status | X | | |
| Employment situation | X | | |
| Household income | X | | |

**Objective Test Variables**

**Protocol**: 1 or 2, depending on if it is the old or the new protocol. Change dates and specifications on the Definitions and Protocols document.

***NFR Threshold Phase***

**NFR threshold**: the average level of stimulation (0-60mA) at which the reflex is detected. Usually the software outputs a number at the end of the test. If it does not happen, we calculate the same way the software does but only with the available reflexes (including the first).

**Mean Pain Rating at NFR Threshold**: the average pain rating (0-100) at which the reflex is detected. Usually the software outputs a number at the end of the test. If it does not happen, we calculate the average of the pain ratings at which a reflex was detected.

**Number of reflexes achieved**: the total number of times that a reflex was detected ("1" on column "Reflex-0,1").

**Intensity of the first reflex**: the single level of stimulation (0-60mA) at which the first reflex was detected. There is always only one value per test.

**Area under the NFR curve**: the total area under the curve created by the level of stimulation in mA (X axis) and the NFR in uV (Y axis) columns. The total AUC can be calculated by the sum of each interval between two consecutive values: $\sum [0.5*(Y_{n+1}+Y_n)*(X_{n+1}-X_n)]$. Please see attached example for clarification.

**Mean baseline activity before the first reflex**: the average muscle baseline electrical activity, previous to of each the stimuli, until the very first reflex is found (including this row). If no reflex is detected, we just consider the whole test.

**Mean baseline activity after the first reflex**: the average muscle baseline electrical activity, previous to of each the stimuli, after the very first reflex is found (not including this row). If no reflex is detected, we do not consider this variable (unknown).

**Endpoint**: the reason why the test ended. Alternatives are: 0 – NFR threshold/classic summation detected; 1 – pain rating >= 95; 2 – aborted

***Summation Phase***

**Number of classic summations detected**: <u>total number</u> of classic summations detected per one full evaluation. Classic summation is defined by the presence of 2 or 3 reflexes among the last 3 stimuli and no reflexes between the first 2 stimuli at each block. Please see attached example for clarification. <u>Caution</u>: the software actually reads summation even when there are reflexes in the first half of the block. Therefore, there might be a mismatch in the number of true classic summations and the number of summations detected by the software.

**Classic summation threshold**: the <u>average</u> level of stimulation (0-40mA) at which a classic summation was detected.

**First classic summation intensity**: the <u>level of stimulation</u> (0-40mA) at which a classic summation is first detected per one full evaluation.

**First block with classic summation**: the number of the first block to show this phenomenon.

**Number of amplitude summations detected**: total number of amplitude summations detected per one full evaluation. Amplitude summation is present when the difference between the highest NFR value (uV) among the last 3 stimuli and the lowest NFR value (uV) between the first 2 stimuli at each block is equal to or greater than 1 Average Baseline Standard Deviation [Avg BaseSD (uV)]. Please see attached example for clarification. To have an amplitude summation, the phenomenon called "summation baseline activity increment" must be absent.
**Amplitude summation threshold**: the average level of stimulation (0-40mA) at which an amplitude summation was detected.
**First amplitude summation intensity**: the level of stimulation (0-40mA) at which an amplitude summation is first detected per one full evaluation.
**First block with amplitude summation**: the number of the first block to show this phenomenon.
**Number of pain summations detected**: total number of pain summations detected per one full evaluation. Pain summation is present when the difference between the highest pain rating (0-100) among the last 3 stimuli and the lowest pain rating (0-100) between the first 2 stimuli at each block is equal to or greater than 3. Please see attached example for clarification. Bear in mind that pain summation may be falsely detected when the tester rates 95 or higher at the last stimuli, respecting the decision of the participant to no longer proceed with that level of stimulation (*e.g.*, 40-40-40-40-95).
**Pain summation threshold**: the average level of stimulation (0-40mA) at which a pain summation was detected.
**First pain summation intensity**: the level of stimulation (0-40mA) at which a pain summation is first detected per one full evaluation.
**First block with pain summation**: the number of the first block to show this phenomenon.
**Number of summation baseline activity increment detected:** total number of blocks presenting with baseline activity increment in the summation phase.
**Summation baseline activity increment**: the level of stimulation (0-40mA) at which a baseline activity increment was first detected before each turning point/final stop. Baseline activity increment in the summation phase is present when the difference between the last and the first stimuli baseline activity [on column "Base (uV)"] is equal to or greater than 1 Average Baseline Standard Deviation [Avg BaseSD (uV)]. Please see attached example for clarification. The presence of increase in baseline activity excludes the detection of the called "amplitude summation" at the same block. If more than 1 baseline increment is detected, the average level of stimulation will be reported.
**First summation baseline activity increment detected**: level at which the first baseline activity increment was detected in the summation phase.
**First block with baseline activity increment**: the number of the first block to show this phenomenon.

**Self-Report Variables**

**Fibromyalgia impact questionnaire (FIQ)**

Score range: 0-100.
Meaning: average fibromyalgia patients score 50, severe patients score 70 and above.
Scoring system:

| Scale | Item # | Question # | Reverse | Score Range | Normalization |
|---|---|---|---|---|---|
| Physical impairment | 1 | 1-11* | No | 0 - 3 | S X 3.33 |
| Feel good | 2 | 12 | Yes | 0 - 7 | S X 1.43 |
| Work missed | 3 | 13 | No | 0 - 7 | S X 1.43 |

| | | | | | |
|---|---|---|---|---|---|
| Do work | 4 | 14 | No | 0 - 10 | None |
| Pain | 5 | 15 | No | 0 - 10 | None |
| Fatigue | 6 | 16 | No | 0 - 10 | None |
| Rested | 7 | 17 | No | 0 - 10 | None |
| Stiffness | 8 | 18 | No | 0 - 10 | None |
| Anxiety | 9 | 19 | No | 0 - 10 | None |
| Depression | 10 | 20 | No | 0 - 10 | None |

**physical impairment score is obtained by calculating the average of the answered questions (0-3).*

**Brief pain inventory (BPI)**

Score range: 0-10.

Meaning: 0-4 mild, 5-6 moderate, 7-10 severe pain.

Scoring system: average of first 4 items (BPI pain severity) and item 7 (average of 7 sub-items; BPI pain interference). Besides BPI intensity (first 4 questions) and BPI interference (last 7 questions), we are also going to analyze BPI global pain (average of both, ranging also from 0 to 10)

**SF-36 vitality**

Score range: 0-100.

Meaning: the higher the score, the better the quality of life. The vitality scale can be an instrument of fatigue.

Scoring system: Raw score range 4-24. Four questions (ranging 1-6 each). Questions 3 and 4 are directly scored (1=1… 6=6) and questions 1 and 2 are reversely scored (1=6… 6=1). Transformed vitality scale (0-100) = [(Actual raw score – 4) / 20] x 100. Update on reverse scoring after running analyses. Therefore, brush off obtained numbers as of 3/27/09.

**Sleep-related questionnaire (Insomnia severity index – ISI)**

Score range: 0-28

Meaning: 0-7 = No clinically significant insomnia, 8-14 = Subthreshold Insomnia, 15-21 = Clinical Insomnia (moderate severity), 22-28 = Clinical Insomnia (severe)

Scoring system: total score is the sum of each answer.

**Multiple ability self-report questionnaire (MASQ)**

Score range: 38-190 (38 questions, 1-5 each)

Meaning: higher scores reflect more self-reported cognitive dysfunction

Scoring system: reverse score (R) (1=5, 2=4, 3=3, 4=2, 5=1) items 2, 6, 8, 9, 10, 17, 22, 23, 24, 26, 28, 29, 30, 31, 33, 36, 37. Calculate subscales:

Language= sum (1,R2,3,4,5,R6,7,R8)
Visual Perceptual Ability= sum (R9,R10,11,12,13,14)
Verbal Memory= sum (15,16,R17,18,19,20,21,R22)
Visual Spatial Memory= sum (R23,R24,25,R26,27,R28,R29,R30)
Attention Concentration= sum (R31,32,R33,34,35,R36,R37,38)
There is no total score.

**Pain-related thoughts and feelings** (Pain catastrophizing scale)

Score range: 0-52 (13 questions, 0-4 each)

Meaning: higher scores represent more intense catastrophizing.

Scoring system: sum of each question

**Patient health questionnaire-8 (PHQ-8)**

Score range: 0-24 ranges.

Meaning: 5-9 = mild, 10-14 = moderate, 15-19 = moderately severe, and 20-24 = severe depression.

Scoring system: sum of answers (8 questions: 0, 1, 2, or 3)

**Anger Expression Scale (AES)**

Spielberger, C. D., Johnson, E. H., Russell, S. F.,Crane, R. J., Jacobs, G. A., & Worden, T. J. (1985). The experience and expression of anger: Construction and validation of an anger expression scale. In M. A. Chesney, & R. H. Rosenman (Eds.), *Anger and hostility in cardiovascular and behavioral disorders* (pp. 5–30). Washington, DC: Hemisphere

Score range: 20-80 (20 questions, 1-4 each)

Meaning: the higher the score the higher the anger level.

Scoring system: sum of each item. No reverse scoring necessary.

The Anger Expression Scale (Spielberger et al., 1985) assesses how one acts when one is angry. Scales (and items) include: anger-in ("I keep things in"), anger-out ("I lose my temper"), and anger-control ("I keep my cool").

```
LET item$(1) = "1. I control my temper."
LET item$(2) = "2. I express my anger."
LET item$(3) = "3. I keep things in."
LET item$(4) = "4. I make threats I don't mean to carry out."
LET item$(5) = "5. I pout or sulk."
LET item$(6) = "6. I withdrew from people."
LET item$(7) = "7. I make sarcastic remarks to others."
LET item$(8) = "8. I keep my cool."
LET item$(9) = "9. I do things like slamming doors ."
LET item$(10) = "10. I boil inside, but I don't show it."
LET item$(11) = "11. I argue with others."
LET item$(12) = "12. I tend to harbor grudges that I don't tell anyone about."
LET item$(13) = "13. I strike out at whatever infuriates me."
LET item$(14) = "14. I am secretly critical of others."
LET item$(15) = "15. I am angrier than I am willing to admit."
LET item$(16) = "16. I calm down faster than most other people do."
LET item$(17) = "17. I say nasty things."
LET item$(18) = "18. I am irritated a great deal more than people are aware
of."
LET item$(19) = "19. I lose my temper."
LET item$(20) = "20. If someone annoys me, I am apt to tell him/her how I
feel."
angerin = a(3) + a(5) + a(6) + a(10) + a(12) + a(14) + a(15) + a(18)
angerout = a(2) + a(7) + a(9) + a(11) + a(13) + a(17) + a(19) + a(20)
angersum = angerin + angerout + a(1) + a(4) + a(8) + a(16)
```

**Anxiety questionnaire**:

Score range: 20-80.

Meaning: higher scores represent greater levels of anxiety *state*

Scoring system: sum of each answer. Reverse scoring (1=4…, 4=1) at questions: 1, 2, 5, 8, 10, 11, 15, 16, 19, 20.

## Clinical Variables

**Height:** in cm.

**Weight**: in Kg.

**Blood pressure**: in mmHg.

**Year of pain onset**: the year in which the first pain attributed to fibromyalgia started.

## Health Care Utilization Variables

**Pain clinic:** have you ever been seen in a pain clinic? Never (0), yes, but not now (1), yes, currently (2).

**Counselor, psychologist, psychiatrist**: have you ever been seen (treated) by a counselor, psychiatrist, or psychologist? Never (0), yes, but not now (1), yes, currently (2).
**Other treatments**: physical therapy, chiropractor, acupuncture, massage, any other practitioners or had other treatments (besides medicines) for pain (name which). Five different questions with the following alternatives: never (0), yes, but not now (1), yes, currently (2). And also one question regarding a specialist consultation with the following options: neurologist, orthopedist, rheumatologist, other specialist doctor (name which).
**Pain level follow-up (Global Pain Assessment)**: overall body pain level since the beginning of the study. Worse, about the same, or better. If better, a little better (1), somewhat better (2), moderately better (3), a lot better (4), completely better (pain is gone) (5).
**Medication discontinued***: Y/N and name.
**Medication dose change***: Y/N and description.
**Medication frequency change***: Y/N and description.
**New medication**:* Y/N and name.
**Medications can be categorized into the 11 following classes:*
1. Anti-convulsants: gabapentin, neurontin, lyrica, pregabalin
2. Tri-cyclics: doxepin, sinequan, amitriptyline (elavil), nortriptyline (pamelor)
3. SSRI anti-depressant: fluoxetin (Prozac), paxil, sertraline (zoloft), celexa, lexapro, luvox
4. SNRI anti-depressant: venlafaxine (effexor), duloxetine (cymbalta),
5. Other anti-depressant: remeron, bupropion (wellbutrin), trazodone (desyrel)
6. Muscle relaxants: cyclobenzaprine (flexeril), skelaxin, robaxin (methocarbamol), carisoprodol (soma), zanaflex (tizanidine), norflex (orphenadrine)
7. NSAIDs: celebrex, naproxen (aleve, anaprox), ibuprofen (motrin, advil), voltaren (cataflam, arthrotec, diclofenac), daypro (oxaprozin), relafen (nabumetone), sulindac (clinoril), mobic (meloxicam), trilisate (trisalicylate), aspirin
8. Simple analgesic: tylenol (acetaminophen)
9. Narcotics: percocet (oxicontin, oxycodone, roxicet, tylox), vicodin (hydrocodone, lortab), darvocet (darvon, propoxyphene), tylenol with codeine, fentanyl (duragesic patch), morphine (MS contin)
10. Semi-narcotic: tramadol (ultram, ultracet)
11. Dopamine agonist: pramipexole (Mirapex), ropinirole (Requip)

**Demographical Variables**

**Date of birth**: mm, dd, yy
**Age at study enrollment**: in years old.
**Educational level:** 8th grade or less, some high school, high school or ged, technical trade or business school, 2-year college degree or some college, 4-year college degree, post-graduate degree (*e.g.*, masters or doctorate), don't know or refused to answer.
**Race**: self-reported. white (caucasian), black or african american, hispanic, spanish or latino, american indian or alaska native, asian, other (specify), don't know or refused to answer
**Gender**: male, female.
**Marital status:** married, divorced, widowed, separated, never married, a member of an unmarried couple, don't know or refused to answer.
**Employment situation**: employed for wages, self-employed, out of work for more than 1 year, out of work for less than 1 year, homemaker, student, retired, unable to work (for health or disability reasons), other, don't know or refused to answer.
**Household income**: comfortable, just enough to make ends meet, not enough to make ends meet, don't know or refused to answer.