PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of a specific training program on the neuromodulation of pain in female fibromyalgia patients (DouFiSport): A 24-month, controlled, randomised, double-blind protocol
AUTHORS	Le Fur Bonnabesse, Anais; Cabon, Mathilde; L'Heveder, Gildas; Kermarrec, Aurélie; Quinio, Bertrand; Woda, Alain; Marchand, Serge; Dubois, Amandine; Giroux-Metges, Marie-Agnes; Rannou, Fabrice; Misery, Laurent; Bodéré, Céline

VERSION 1 – REVIEW

REVIEWER	william b. karper university of north carolina at greensboro
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	--Much English editing is necessary. --Describe any direct pathways between "rebalancing" stress axis mechanisms and "rebalancing" the autonomic nervous system. --What are the mechanisms which help to explain why exercise would be expected to "rebalance" the neurovegatative system? Isn't this system made up of more than just sympathetic and parasympathetic action? --Reference that exercise training will actually affect central neuroplasticity? --What is a "bio-psycho-social care"? Please define. --Describe the stimulation test in detail. How does it correlate with generalized fibromyalgia pain? --More information about the pilot study is needed---number of subjects, analysis of data, etc? --Regarding study non-inclusion factors----what about taking supplements (herbal medicinals, performance enhancing substances, etc.)? --What is the non-vegatative exercise intensity goal? --Active training group protocol is unclear---define "fundamental endurance" and how it will be associated with interval training----define high frequency. --How will VO2 max and HR max be calculated after 24 months? --How will phone calls help with compliance---please reference? How will subjects be encouraged during follow-up? --How will training be "diversified" and kept equal? --Please justify using HIIT with a fibromyalgia group especially since a growing literature appears to support allowing people to

	select their own exercise intensity when adherence/compliance is a concern, let alone those with chronic pain. --How will the difference in fibromyalgia burden between those 18 and 50 years old affect your interpretation of the data? --How will you verify that subjects are complying on the "independent" exercise days?

REVIEWER	Giorgos K. Sakkas Plymouth Marjon University, UK
REVIEW RETURNED	31-May-2018

GENERAL COMMENTS	This is a very interesting protocol with high clinical significance in ameliorating pain symptoms and severity in patients with Fibromyalgia. My main concerns are listed below: The duration of the project is 2 years. This is very important in terms of assessing the effectiveness of the intervention however, the same time the Control group is going to spend two years in a intervention that possibly will not improve their health and pain status. This need to be addressed and possibly include a mid point effectiveness assessment (9 months). If the results are positive, you should use a cross over design and let the Control group participate in the exercise intervention. The drop out rate has been underestimated. The authors need to elaborate more justifying their expected rates. I am expecting a 40-50% drop out rate in two years especially in the Control group. The terms used for characterizing the two groups are not accurate. Active vs Control is not appropriate when both are going to participate in an exercise training session and in addition, the <50% is not the current clinical practice to be considered as standard approach. Since exercise is going to be individualized, the authors should use the “Heart Rate Reserve (HRR)” equation for the calculation of the exercise zone instead of Age adjusted maximum heart rate (HRmax). How training adherence is going to be monitored? Why exercise training is going to be supervised by a physiotherapist? Is physiotherapist appropriately trained to supervise an exercise trial? You should have a specialized clinical exercise physiologist to oversee the project and training adherence. This way you will maximize the effectiveness of the intervention.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: William B. Karper

- Much English editing is necessary.

Authors’ response:
This article has been edited and proofread by the translation service of the University of Western Brittany (France).

- Describe any direct pathways between "rebalancing" stress axis mechanisms and "rebalancing" the autonomic nervous system.

Authors' response:
The stress axis includes the autonomic nervous system and the corticotropic axis. When the stress axis is rebalanced, both the neurovegetative system and the corticotropic axis are rebalanced.

- What are the mechanisms which help to explain why exercise would be expected to "rebalance" the neurovegatative system?

Authors' response:
Physical activity (depending on duration and intensity) gradually and differentially mobilises both the parasympathetic and the sympathetic systems. Neurovegetative dystonia has been found in FM patients (an increased sympathetic response and decreased parasympathetic tone) (1,2). Specific exercise leads to a chronic reduction in sympathetic activity and increased parasympathetic tone (2)(3)(4).

1. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217-27.
2. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
3. Grant CC, Mongwe L, Janse van Rensburg DC, Fletcher L, Wood PS, Terblanche E, et al. The Difference Between Exercise-Induced Autonomic and Fitness Changes Measured After 12 and 20 Weeks of Medium-to-High Intensity Military Training. J Strength Cond Res. sept 2016;30(9):2453-9.
4. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848-54.

- Isn't this system made up of more than just sympathetic and parasympathetic action?

Authors' response:
Mechanisms and structures involved in the activation and regulation of the neurovegetative system could interact with the central nervous system. Central relationships between the neurovegetative system and, the motor cortex, the limbic system, the hypothalamus, the pituitary gland, and the basal ganglia will result in release of analgesic neurotransmitters such as adrenergic neurotransmitters (noradrenalin), serotonin and endogenous opioid (5)(6). This release of neurotransmitters due to exercise leads to increased endogenous inhibition and therefore decreases diffuse pain in FM (5). Central nervous system plasticity induced by physical training could regulate both cardiovascular adaptations (4) and endogenous pain control mechanisms (7)(8).

4. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848-54.
5. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. Pain Rep. sept 2017;2(5):e618.
6. Da Silva Santos R, Galdino G. Endogenous systems involved in exercise-induced analgesia. J Physiol Pharmacol Off J Pol Physiol Soc. févr 2018;69(1):3-13.
7. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817-25.
8. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369-70.

- Reference that exercise training will actually affect central neuroplasticity?

Authors' response:
As seen above, central nervous system plasticity induced by physical training could regulate both cardiovascular adaptations (4) and endogenous pain control mechanisms (7)(8).

4. Martins-Pinge MC. Cardiovascular and autonomic modulation by the central nervous system

after aerobic exercise training. Braz J Med Biol Res Rev Bras Pesqui Médicas E Biológicas Soc Bras Biofísica Al. sept 2011;44(9):848-54.
5. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. Pain Rep. sept 2017;2(5):e618.
6. Da Silva Santos R, Galdino G. Endogenous systems involved in exercise-induced analgesia. J Physiol Pharmacol Off J Pol Physiol Soc. févr 2018;69(1):3-13.
7. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817-25.
8. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369-70.

- What is a "bio-psycho-social care"? Please define.

Authors' response:
A bio-psycho-social care is a "Whole Person Care". All patients attending the pain centre of the university hospital of Brest receive overall and coordinated care. The bio-psycho-social approach takes into account the effects of biological, psychological, and social factors on health. An interdisciplinary team (including chronic pain specialists: psychologist, psychiatrists, anaesthetist, paediatrician, algologist, nurse, etc.) follows up with patients. The bio-psycho-social care in the pain centre is the same for both patients included and patients not included in the study.

- Describe the stimulation test in detail. How does it correlate with generalized fibromyalgia pain?

Authors' response:
Acute pain stimuli trigger pain perception. Several studies show that fibromyalgia patients are deficient in endogenous pain inhibitory systems (significant increases of temporal summation and decreases of conditioned pain modulation) in FM associated with hyperalgesia and allodynia (9)(10)(11). The stimulation test was described in detail by Tousignant-Laflamme and Marchand (2008) (12). This stimulation test assessed endogenous pain mechanisms (diffuse noxious inhibitory controls, temporal summation and perception of pain). Physical activity could rebalance the neurovegetative system and therefore decrease allodynia and hyperalgesia in FM. This stimulation test will assess the impact of this specific training on diffuse noxious inhibitory controls, temporal summation, and perception of pain.

9. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1-2):295-302.
10. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain. sept 1997;13(3):189-96.
11. O'Brien AT, Deitos A, Triñanes Pego Y, Fregni F, Carrillo-de-la-Peña MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. J Pain Off J Am Pain Soc. 15 févr 2018;
12. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73-9.

- **More information about the pilot study is needed---number of subjects, analysis of data, etc?**

Authors' response:
In this pilot study, 89 FM women were divided into 3 groups according to the training performed. Active group (n = 30): Undertook three sessions of 45 minutes of MICT: 65-74% HRmax per week (specific training request). Semi-Active group (n = 28): Undertook 3 sessions of aerobic exercise per week but with a weak intensity. Passive group (n = 31): No completion of training. In each group, pain, quality of sleep, fibromyalgia impact (FIQ), painkiller-grade, anxiety and depression (HAD) was evaluated each year from 2004 to 2009. Improvement of all symptoms was observed in patients of the Active group compared to those of the two other groups. Increasing exercise intensity seems to have increased the effects already obtained through the basic endurance. For patients in the Semi-Active group, a significant change in FIQ and HAD parameters was observed. But there was no significant reduction in

pain or changes in sleep quality in these patients. No effect was observed on the various parameters in patients in the Passive group. Results of this study are currently being published.

- Regarding study non-inclusion factors----what about taking supplements (herbal medicinals, performance enhancing substances, etc.)?

Authors' response:
Any new treatment that could increase performance (mechanisms like doping) is forbidden during the study. Herbal medicinals (non-evidence-based medicine active on performance) are authorized.

- What is the non-vegetative exercise intensity goal?

Authors' response:
The exercise intensity goal in control group is <50% HRmax. This exercise has no effect on the neurovegetative system.

- **Active training group protocol is unclear---define "fundamental endurance" and how it will be associated with interval training----define high frequency.**

Authors' response:
We agree with the reviewer. Fundamental endurance is aerobic exercise performed continuously to raise the heart rate and breathing rate for a prolonged period. Fundamental endurance is only used to start the training. We have changed the active training group protocol in the text.

- How will VO2 max and HR max be calculated after 24 months?

Authors' response:
$V\dot{O}_2$max and HRmax are not calculated after 24 months. Improvement of $V\dot{O}_2$max and HRmax are not an objective of this study. $V\dot{O}_2$max and HRmax are used to adapt the specific training program for each patient.

- How will phone calls help with compliance---please reference? How will subjects be encouraged during follow-up?

Authors' response:
Several studies have assessed the effects of telemonitoring on patients' compliance (13)(14). Phone calls are a simple method of improving adherence in disease management (14) and to enhance home exercise training and physical activity (13).

13. Franke K-J, Domanski U, Schroeder M, Jansen V, Artmann F, Weber U, et al. Telemonitoring of home exercise cycle training in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2821-9.
14. Yasmin F, Banu B, Zakir SM, Sauerborn R, Ali L, Souares A. Positive influence of short message service and voice call interventions on adherence and health outcomes in case of chronic disease care: a systematic review. BMC Med Inform Decis Mak. 22 avr 2016;16:46.

- How will training be "diversified" and kept equal?

Authors' response:
The training will be diversified according to the patient's wishes, ability and experience (swimming, running, zumba, monofin, etc.) (15). The systematic autorecording of HR during the activity will keep the training equal.

15. Fitzcharles M-A, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Manag. juin 2013;18(3):119-26.

- Please justify using HIIT with a fibromyalgia group especially since a growing literature appears to support allowing people to select their own exercise intensity when adherence/compliance is a concern, let alone those with chronic pain.

Authors' response:
HIIT allows the training to work on both the parasympathetic and sympathetic systems. This program is individualized to each patient based on their pain level and their capacity for physical exertion. Only after 6 to 9 months of training and according to their rhythm, abilities, and limits, patients could gradually increase their exercise intensity. HIIT increases exercise intensity and diversifies training sessions. Our pilot study shows that increasing exercise intensity seems to have increased the effects on pain already obtained through MICT. In this study, HIIT (working on the sympathetic system) has lead to a decrease of 4 pain points using a 10-point visual analog scale, and to an improvement in sleep quality. Moreover, authors have shown that moderate and vigorous aerobic exercise reduce perception and that vigorous exercise produces a greater effect (7). Higher training levels are associated with a decrease of pain facilitation and an increase of pain inhibition (8).

7. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817-25.
8. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369-70.

- How will the difference in fibromyalgia burden between those 18 and 50 years old affect your interpretation of the data?

Authors' response:
Patient's age is not a contributor for fibromyalgia burden. This program is individualized and adapted to be consistent with the patient's age and abilities. The pain duration will be assessed during the inclusion visit. Fibromyalgia burden will be assessed with the French version of the Fibromyalgia Impact Questionnaire (FIQ) (16) which assesses the impact of fibromyalgia in everyday life.

16. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728-33.

- How will you verify that subjects are complying on the "independent" exercise days?

Authors' response:
Subjects will note the characteristics (frequency, duration, intensity, type of activity, and supervision) of each training session (both supervised and independent) in a specific training logbook. The physiotherapist will frequently ask patients about their independent training session to provide advice and to motivate them. Moreover, phone calls will assess the compliance of the independent training sessions.

Reviewer 2: Giorgos K. Sakkas

This is a very interesting protocol with high clinical significance in ameliorating pain symptoms and severity in patients with Fibromyalgia.
My main concerns are listed below:

The duration of the project is 2 years. This is very important in terms of assessing the effectiveness of the intervention however, the same time the Control group is going to spend two years in a intervention that possibly will not improve their health and pain status. This need to be addressed and possibly include a mid point effectiveness assessment (9 months). If the results are positive, you should use a cross over design and let the Control group participate in the exercise intervention.

Authors' response:
We agree with the reviewer. Our objective is to validate a specific training active on the neurovegetative system. Subjects who have obtained an important decrease in their symptoms due to active training

will tend to continue this training on their own initiative (limit of crossover). A mid point assessment is planned between 6 and 9 months of training according to the patients' rhythm, abilities, and limits. Improvement in both control and active groups are expected in quality of life (FIQ, HADS). Pain and sleep improvement expected only in active group may take some time (2 years in our pilot study) to obtain.

The drop out rate has been underestimated. The authors need to elaborate more justifying their expected rates. I am expecting a 40-50% drop out rate in two years especially in the Control group.

Authors' response:
Our pilot study over 5 years shows a 15 % drop out rate. This study protocol could be a burden for patients and we agree that this drop out rate may be low. The feasibility of this study could not be considered for our structure if the drop out rate were 40-50%. In parallel to study visits, patients are frequently followed up at the pain centre of the university hospital of Brest for global and coordinated care (bio-psycho-social care). Regular follow-up allows us to limit the drop out rate.

The terms used for characterizing the two groups are not accurate. Active vs Control is not appropriate when both are going to participate in an exercise training session and in addition, the <50% is not the current clinical practice to be considered as standard approach.

Authors' response:
We agree with the reviewer and we have changed "Control" to "Semi-Active".

Since exercise is going to be individualized, the authors should use the "Heart Rate Reserve (HRR)" equation for the calculation of the exercise zone instead of Age adjusted maximum heart rate (HRmax).

Authors' response:
We agree with the reviewer. However from mathematical modelling, researchers found that the Tanaka's age-based prediction equation (208-0.7×age) could adequately predict the maximum heart rate (HRmax) for people with fibromyalgia (17)(18). After 6-9 months of training, a maximal-effort graded exercise test will determine HRmax and $V\dot{O}_2max$ for each patient.

17. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358-67.
18. Lemos MCD, Valim V, Zandonade E, Natour J. Intensity level for exercise training in fibromyalgia by using mathematical models. BMC Musculoskelet Disord. 22 mars 2010;11:54.

How training adherence is going to be monitored?

Authors' response:
Subjects will note characteristics (frequency, duration, intensity, type of activity, and supervision) of each training session (supervised and independent) in a specific training logbook. Physiotherapists will frequently ask patients about their independent training session to provide advice and to motivate them. Phone calls and follow-up at the pain centre will assess the compliance with the training protocol.

Why exercise training is going to be supervised by a physiotherapist? Is physiotherapist appropriately trained to supervise an exercise trial? You should have a specialized clinical exercise physiologist to oversee the project and training adherence. This way you will maximize the effectiveness of the intervention.

Authors' response:
In France, physiotherapists are trained at school to oversee training rehabilitation. In this study, physiotherapists are specially trained in high level athlete physiology and coaching, in chronic pain, in

training rehabilitation and specially trained for this study protocol. This protocol study has been devised with physiologists of the university hospital of Brest (MA Giroux-Metges and F Rannou).

Bibliography

1. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin Arthritis Rheum. févr 2000;29(4):217-27.
2. da Cunha Ribeiro RP, Roschel H, Artioli GG, Dassouki T, Perandini LA, Calich AL, et al. Cardiac autonomic impairment and chronotropic incompetence in fibromyalgia. Arthritis Res Ther. 2011;13(6):R190.
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5. Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. Pain Rep. sept 2017;2(5):e618.
6. Da Silva Santos R, Galdino G. Endogenous systems involved in exercise-induced analgesia. J Physiol Pharmacol Off J Pol Physiol Soc. févr 2018;69(1):3-13.
7. Naugle KM, Naugle KE, Fillingim RB, Samuels B, Riley JL. Intensity thresholds for aerobic exercise-induced hypoalgesia. Med Sci Sports Exerc. avr 2014;46(4):817-25.
8. Law LF, Sluka KA. How does physical activity modulate pain? Pain. 2017;158(3):369-70.
9. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain. mars 2005;114(1-2):295-302.
10. Lautenbacher S, Rollman GB. Possible deficiencies of pain modulation in fibromyalgia. Clin J Pain. sept 1997;13(3):189-96.
11. O'Brien AT, Deitos A, Triñanes Pego Y, Fregni F, Carrillo-de-la-Peña MT. Defective Endogenous Pain Modulation in Fibromyalgia: A Meta-Analysis of Temporal Summation and Conditioned Pain Modulation Paradigms. J Pain Off J Am Pain Soc. 15 févr 2018;
12. Tousignant-Laflamme Y, Pagé S, Goffaux P, Marchand S. An experimental model to measure excitatory and inhibitory pain mechanisms in humans. Brain Res. 16 sept 2008;1230:73-9.
13. Franke K-J, Domanski U, Schroeder M, Jansen V, Artmann F, Weber U, et al. Telemonitoring of home exercise cycle training in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:2821-9.
14. Yasmin F, Banu B, Zakir SM, Sauerborn R, Ali L, Souares A. Positive influence of short message service and voice call interventions on adherence and health outcomes in case of chronic disease care: a systematic review. BMC Med Inform Decis Mak. 22 avr 2016;16:46.
15. Fitzcharles M-A, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Manag. juin 2013;18(3):119-26.
16. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol. mai 1991;18(5):728-33.
17. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. oct 2011;15(5):358-67.
18. Lemos MCD, Valim V, Zandonade E, Natour J. Intensity level for exercise training in fibromyalgia by using mathematical models. BMC Musculoskelet Disord. 22 mars 2010;11:54.

VERSION 2 – REVIEW

REVIEWER	william b. karper University of North Carolina at Greensboro Grensboro, NC, USA
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	Have paper reviewed for proper English usage---verb tense. Everything looks good. I would suggest using the Karvonen

	formula for setting intensity of exercise versus age-adjusted heart rate. Also, exercising at 65% to 75% of HR max may move some subjects into the vigorous intensity range. I would use 55%-65%. Be careful with the HIIT with this group-----your plan is pretty intense. You may get severe DOMS.

VERSION 2 – AUTHOR RESPONSE

1/Have paper reviewed for proper English usage---verb tense.

Authors' response:
English usage in this article has been edited and the text proofread.

2/Everything looks good.

Authors' response:
We thank the reviewer for this comment.

3/ I would suggest using the Karvonen formula for setting intensity of exercise versus age-adjusted heart rate.

Authors' response:
We agree with the reviewer, but from mathematical modelling, researchers found that Tanaka's age-based prediction equation (208 − 0.7×age) could adequately predict maximum heart rate (HRmax) for persons with fibromyalgia (1,2). After 6–9 months of training, a maximal-effort graded exercise test will determine HRmax and V̇O2max for each patient.

1. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, et al. Exercise therapy for fibromyalgia. Curr Pain Headache Rep. 2011 Oct;15(5):358–67.
2. Lemos MCD, Valim V, Zandonade E, Natour J. Intensity level for exercise training in fibromyalgia by using mathematical models. BMC Musculoskelet Disord. 2010 Mar 22;11:54.

4/ Also, exercising at 65% to 75% of HR max may move some subjects into the vigorous intensity range. I would use 55%-65%.
Authors' response:

We understand the reviewer's comment. Our goal is to differentiate the two groups (active and semi-active). The only difference between groups is the training intensity, and this difference has to be substantial. In the semi-active group, LICT will have no effect on the neurovegetative system. In the active group, MICT and especially HIIT will have effects on the both parasympathetic and sympathetic systems. We drew on Bidonde et al. (2014) in a review of reviews about exercise for adults with fibromyalgia (3), which defines four levels of training intensity:
- Very light intensity: <57 %HRmax
- Light intensity: 57-63 %HRmax
- Moderate intensity: 64-76 %HRmax
- Vigorous intensity: 77-95 %HRmax

3. Bidonde J, Busch AJ, Bath B, Milosavljevic S. Exercise for adults with fibromyalgia: an umbrella systematic review with synthesis of best evidence. Curr Rheumatol Rev. 2014;10(1):45–79.

5/ Be careful with the HIIT with this group-----your plan is pretty intense. You may get severe DOMS.

Authors' response:
To promote adherence of our patients and to limit pain exacerbation, exercise intensity will start very low and then will increase very gradually to reach the neurovegetative goal (4). The time required to achieve this goal may be several weeks, months, even several years (according to the patient's pace, abilities, and limits). The intensity of the training in expected to play an essential role in the modulation of the autonomic nervous system (5,6). Our pilot study and literature have shown that high intensity training leads to more autonomic adaptations (7) than moderate intensity exercise: HIIT should be more efficacious than MICT alone in reducing pain and FM symptoms. A maximal effort test (VO2max, HRmax) and a cardiovascular check-up will be made before HIIT to optimize training intensity for each patient.

4. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. 2010 Oct;151(1):77–86.
5. Cornelissen VA, Verheyden B, Aubert AE, Fagard RH. Effects of aerobic training intensity on resting, exercise and post-exercise blood pressure, heart rate and heart-rate variability. J Hum Hypertens. 2010 Mar;24(3):175–82.
6. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, et al. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. Eur Heart J. 2016 Aug 1;37(29):2307–13.
7. Alansare A, Alford K, Lee S, Church T, Jung HC. The Effects of High-Intensity Interval Training vs. Moderate-Intensity Continuous Training on Heart Rate Variability in Physically Inactive Adults. Int J Environ Res Public Health. 2018 Jul 17;15(7):1508.