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1 **The application of neuromuscular electrical stimulation (NMES) in cancer rehabilitation:**
2 **current prescription, pitfalls, and future directions.**

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27 **Abstract**

28 The plethora of treatment complications associated with cancer can be offset by regular
29 exercise participation; however, adherence to current guidelines is poor, in particular in those
30 unable or not allowed to participate in voluntary exercise due to their underlying disease.
31 Alternative therapies such as neuromuscular electrical stimulation (NMES) are promising
32 although previous results in cancer survivors have been equivocal. This is likely in response to
33 methodological issues such as inappropriate NMES prescription. Therefore, the aim of this
34 commentary is to propose three key areas which should be addressed to increase NMES
35 effectiveness in cancer rehabilitation; 1) NMES exercise should target both the neuromuscular
36 and cardiovascular systems through low and high frequency modalities, 2) technological
37 advancements such as mobile app based systems should be leveraged to improve at-home
38 monitoring of home-based NMES exercise, and 3) prescription and progression should follow
39 the fundamental principles of exercise to overcome the heterogeneity in daily physiological,
40 functional and psychological factors faced by survivors. Addressing these three key areas in
41 future studies may help improve NMES exercise effectiveness and accelerate patient
42 rehabilitation.

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50 **Key Words:** neuromuscular electrical stimulation, rehabilitation, physical function,
51 technology

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53 Annual cancer diagnosis rates (> 10 million per year) are estimated to rise by 50% by 2030 [1].
54 Current antineoplastic treatments are effective, with a year-on-year decline in cancer mortality
55 rates reported in men (-8%) and women (-3%) since 2011 [2]. However, cancer treatments are
56 associated with a plethora of side effects which negatively impact on activities of daily living
57 and quality of life.

58

59 Exercise performed under regular medical supervision is currently recommended to help offset
60 cancer treatment complications such as the loss of muscle strength and cardiorespiratory fitness
61 (CF). Current exercise guidelines recommend 150mins/week of moderate intensity exercise
62 coupled with 2-3 resistance training sessions per week for all cancer survivors [3]. However,
63 only 35% of patients achieve these recommendations [4]. The reduced participation rates
64 among cancer survivors are exacerbated by treatment complications which make voluntary
65 exercise difficult [5] and some patients (e.g. brain and bone metastases) may be excluded from
66 exercise if determined to be at risk of harm [6]

67

68 Alternative therapies such as neuromuscular electrical stimulation (NMES) have the potential
69 to provide an exercise stimulus to such individuals. Studies in patients with advanced disease
70 have demonstrated functional and strength benefits and concluded that NMES is safe and best
71 suited to those unable to perform voluntary exercise [7]. As such, NMES can be performed
72 under regular medical supervision, even in those with severe concomitant disease, with a recent
73 report suggesting physician supervised NMES to be safe even in those with implantable
74 cardioverter defibrillators when delivered to the lower limbs [8]. This makes NMES uniquely
75 placed for cancer survivors.

76

77 Over the past decade there has been a paucity of research investigating the implementation of
78 NMES into cancer rehabilitation. A case study involving a female patient with extensive
79 metastatic cancer which contraindicated voluntary exercise participation, showed
80 improvements in endurance capacity (+44%), functional muscle strength (+20%), self-
81 confidence and independence [9]. However, studies that have implemented home-based NMES
82 exercise have generally had low adherence rates and minimal improvements in functional and
83 strength outcomes [10–12]. The reasons for these findings are unclear, but may be partially due
84 to methodological issues such as inappropriate NMES prescription and a lack of appropriate
85 monitoring. Therefore, the aim of this commentary is to propose key issues which if addressed
86 may help to increase the effectiveness of NMES in these populations. As such, three key areas
87 have been identified:

88

- 89 1. *The use of NMES to target the neuromuscular and cardiovascular systems (termed*
90 *concurrent NMES)*: Research in cancer to date has only implemented high frequency
91 NMES exercise (>50Hz) which is recommended for gains in muscle strength and size,
92 but has negligible effect on CF [13]. Therefore, NMES exercise which can target both
93 strength and CF is required to meet current exercise guidelines. Aerobic NMES
94 exercise protocols incorporating continuous rhythmical contractions at low frequency
95 (4Hz) have been shown to improve CF (VO_{2max} : +10%) in patient groups after 8 weeks
96 [14]. In addition, concurrent protocols involving both a strength (30Hz, 15mins) and an
97 aerobic (4Hz, 45mins) phase within a 60min session have led to improvements in
98 muscle strength (15%) and aerobic exercise capacity (3.5%) over 8 weeks in the elderly
99 [15]. By utilising both high and low frequency NMES exercise, this form of NMES
100 prescription has the potential to meet exercise guidelines, ensure that an unmet clinical

101 need is addressed and possibly accelerate rehabilitation and patient return to voluntary
102 exercise through improved muscle strength and exercise tolerance.

103

104 2. *Leveraging technology for effective home-based monitoring:* Supervised NMES
105 exercise allows for the close monitoring of exercise adherence. However, self-
106 management interventions may improve patient adherence. In addition, patient
107 preferences lean towards home-based NMES exercise [5]. Current data on adherence
108 during home-based NMES has previously been collected using self-report diaries, but
109 a common limitation to this method is over-reporting of exercise levels [16]. Therefore,
110 patients may receive an inadequate exercise dose, possibly masking the true potential
111 of NMES exercise. Home-based NMES exercise could be improved if advancements
112 in digital technology which have revolutionised how we now communicate, access, and
113 monitor information [17] are implemented to help monitor and collect patient data, in
114 addition to providing remote support to patients [18]. Combined with regular physician
115 supervision which can minimise and avoid exercise side effects, technology has the
116 potential to help provide safe, monitored home-based NMES exercise which can
117 improve patient engagement with their own healthcare through self-management and
118 improve patient outcomes.

119

120 3. *Personalised NMES prescription and progression:* A homogenous NMES prescription
121 which is seen in most NMES exercise studies may mask its potential in some users due
122 to the considerable inter-individual heterogeneity which exists between users. In
123 voluntary exercise, four exercise principles (individualisation, specificity, progressive
124 overload, and rest/recovery) have been outlined to improve exercise prescription in
125 cancer [19] but are not conventionally applied to NMES exercise protocols. To target

126 these principles, voluntary exercise programmes systematically manipulate exercise
127 variables (i.e. periodisation) to maximise adaptations [20]. In addition, autoregulation,
128 defined as the ability to alter the magnitude of the exercise stimulus through
129 manipulation of variables such as exercise volume and intensity to match the
130 individual's daily readiness to train [21] has the potential to allow for better monitoring
131 and personalisation of the daily exercise prescription [22]. Considering the
132 heterogeneity in daily physiological, functional and psychological factors, cancer
133 patients may benefit from a similar approach and more personalised NMES protocol
134 design. Designing individually tailored NMES exercise based on these exercise
135 principles may help improve the effectiveness, progression and adherence to NMES
136 exercise.

137

138 In conclusion, to improve the delivery of NMES, it is proposed that we address the challenges
139 mentioned in this commentary. Whilst current NMES exercise demonstrates efficacy in various
140 pathologies, methodological issues in the current NMES/cancer literature combined with the
141 heterogeneity of cancer patients potentially masks the true potential of NMES exercise in
142 patients unable to exercise voluntarily or those in which active exercise is contraindicated.
143 Digital technologies and the application of exercise principles may help significantly improve
144 the clinical effectiveness of NMES and accelerate patient return to activities of daily living and
145 voluntary exercise.

146

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