Commentary

Pharmaceutical Interventions in Chronic Fatigue Syndrome: A Literature-based Commentary

Spencer Richman, B.Sc.[1,2]; Matthew C. Morris, Ph.D.[1,2]; Gordon Broderick, Ph.D.[1,2,3,5]; Travis J.A. Craddock, Ph.D.[3,4,6]; Nancy G. Klimas, M.D.[3,6]; and Mary Ann Fletcher, Ph.D.[3,6]

[1]Gosnell School of Life Sciences, Rochester Institute of Technology, Rochester, NY, USA; [2]Center for Clinical Systems Biology, Rochester General Hospital, Rochester, NY, USA; [3]Institute for Neuro Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL, USA; [4]Departments of Psychology and Neuroscience, Computer Science, Nova Southeastern University, Fort Lauderdale, FL, USA; [5]Department of Biomedical Engineering, Rochester Institute of Technology, Rochester, NY, USA; and [6]Department of Clinical Immunology, Nova Southeastern University, Fort Lauderdale, FL, USA

ABSTRACT

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disorder characterized by prolonged periods of fatigue, chronic pain, depression, and a complex constellation of other symptoms. Currently, ME/CFS has no known cause, nor are the mechanisms of illness well understood. Therefore, with few exceptions, attempts to treat ME/CFS have been directed mainly toward symptom management. These treatments include antivirals, pain relievers, antidepressants, and oncologic agents as well as other single-intervention treatments. Results of these trials have been largely inconclusive and, in some cases, contradictory. Contributing factors include a lack of well-designed and -executed studies and the highly heterogeneous nature of ME/CFS, which has made a single etiology difficult to define. Because the majority of single-intervention treatments have shown little efficacy, it may instead be beneficial to explore broader-acting combination therapies in which a more focused precision-medicine approach is supported by a systems-level analysis of endocrine and immune co-regulation. (*Clin Ther.* 2019;41:798–805)

Keywords: ME/CFS, clinical trials, immune therapy, illness heterogeneity, precision medicine.

INTRODUCTION

The management of complex multifactorial long-term diseases is often marred by a confluence of partially or entirely ineffectual treatments. Due to the many symptoms displayed by those affected, there is very often no single clear path to treatment or symptom management. *Myalgic encephalomyelitis*, also known as *chronic fatigue syndrome* (ME/CFS), is a disease characterized by an inability to exert oneself physically, often coupled with a combination of other symptoms, including sleep disorder, severe unpredictable pain, and compromised cognitive abilities. Those experiencing ME/CFS have prolonged (6 months or greater) periods of exhaustion that is not relieved by rest.[1] The exact etiology of ME/CFS is currently unknown,[2] although multiple hypotheses exist regarding potential triggers and mechanisms of illness, including viral and other forms of infection,[3,4] mitochondrial dysfunction,[5] and neurologic abnormalities.[6–9] Ultimately, there may be no single underlying cause of this illness and it is not improbable that ME/CFS may serve as an umbrella term for multiple different diseases associated with overlapping symptoms.[10] The diversity in symptom profiles and potential etiologies associated with ME/

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CFS make the treatment and management of this illness extremely challenging and a treatment that may be effective for one subset of individuals may not be effective for another.

As a result of this uncertainty regarding the underlying mechanisms of illness in ME/CFS, most attempts at pharmacologic treatment have focused on the reduction in the severity of specific subsets of symptoms. This summary overview delineates a number of the more prominent treatments for ME/CFS into different categories, and evaluates the methods and results of corresponding drug trials (Figure). Drugs including pain relievers (both specific and nonspecific NSAIDs), antidepressants (monoamine oxidase [MAO] inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors), antivirals, and antihistamines have been identified as possibly beneficial in treating ME/CFS. Although other, nonpharmacologic approaches to the treatment of ME/CFS have been considered, such as cognitive-behavioral therapy and graded exercise therapy,[11] we focus in this overview on pharmaceutical agents only.

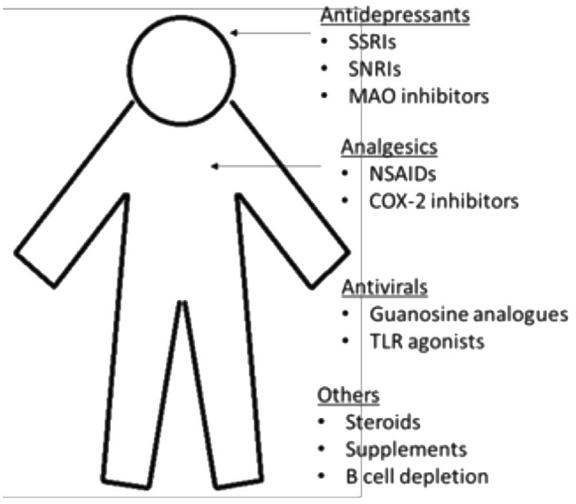

Figure. Pharmacologic interventions in myalgic encephalomyelitis/chronic fatigue syndrome. For the most part, clinical trials have studied antiviral agents, analgesics, and antidepressants, with some additional drugs falling outside of these classes. COX = cyclooxygenase; MAO = monoamine oxidase; SNRI = selective serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TLR = Toll-like receptor.

Antivirals

A viral cause of ME/CFS has been long hypothesized, and there is evidence that both enteroviruses and herpesviruses may be involved in ME/CFS, at least in some cases.[12,13] Over the past 3 decades there has been a significant amount of research into the efficacy of antiviral drugs in the treatment of ME/CFS. These treatments generally include 2 different classes of antivirals, guanosine analogues, such as acyclovir and valacyclovir, and the immunomodulator rintatolimod. Such treatments have met with varying levels of success in clinical trials in patients with ME/CFS.

The first study attempting to treat ME/CFS with acyclovir was published in 1988. A placebo-controlled study in 24 patients with ME/CFS, each given first rapid doses of intravenous acyclovir for 1 week, followed by 1 month of oral administration, found no significant difference in the improvements in individuals between the control and test groups. The study concluded that acyclovir had no noticeable effect in patients with ME/CFS.[14] However, a 2007 study on valacyclovir, which is metabolized into acyclovir on administration, found a significant improvement in physical activity among 27 patients with ME/CFS and elevated Epstein–Barr virus antibodies.[15] However, treatment methods were altered significantly in those who did not respond to valacyclovir treatment alone, complicating the interpretation of the results. Additional drugs, including cimetidine and probenecid, were added to the treatment course in patients not responding within 3 months of treatment. Furthermore, 3 patients who experienced side effects of valacyclovir were placed on treatment with a different guanosine analogue, famciclovir.[15] In addition, administration of these drugs was also not performed at consistent intervals, as treatment was withheld when symptoms appeared to have improved over a month and was re-administered only if a patient began to relapse.[15] These confounding variables leave the effectiveness of valacyclovir/acyclovir in question. A 2013 study by Montoya et al[16] conducted at Stanford University examined another guanosine analogue,

valganciclovir, in 30 patients with ME/CFS and elevated serum immunoglobulin G levels of Epstein–Barr virus and human herpesvirus 6. That study found statistically significant improvements in cognitive function and reduced mental fatigue in patients receiving valganciclovir as compared to placebo, further supporting similar conclusions drawn earlier by the same group in a study in which 75% of patients (9 of 12) who experienced viral CNS dysfunction were found to have "near-resolution of their symptoms" following treatment with valganciclovir.[17] That study was limited by its small sample size but provided evidence for continued research by these and other investigators.

Rintatolimod, a double-stranded RNA drug designed to increase antiviral immune response via Toll-like receptor 3 activation, is one of the only drugs to have been developed with the specific goal of treating ME/CFS.[18,19] A 1995 study by Strayer et al[20] found significant improvements in cognitive function and memory, as well as a reduction in human herpesvirus 6 mRNA expression in 15 patients with ME/CFS who underwent long-term treatment with rintatolimod. In a second, larger-scale clinical trial in 234 patients with severe ME/CFS, results were consistent with those from the earlier trial, although improvements were somewhat reduced in magnitude.[21] Rintatolimod treatment has been associated with improvements in symptom burden in multiple clinical trials,[18] but has generally not been found to produce stable remission, suggesting that further studies are required.

Overall, evidence so far suggests that antiviral drugs appear to be of limited efficacy in treating ME/CFS over a broad demographic. Trials of existing antiviral medications either fail outright or tend to be of imperfect study design and/or low statistical power. Once again, it should be noted that the causes of ME/CFS are likely heterogeneous, meaning that treatments may work in some, but not broadly in all, patients. Future trials of antiviral drugs may benefit greatly from the careful selection of the criteria for the inclusion of patients, especially with respect to seropositivity for specific viruses.

Analgesics

Pain relievers, both over-the-counter and prescription-only, are often used to treat the generalized body pains and aches associated with ME/CFS. A 2009 review by Boneva et al[22] on medication use by patients with ME/CFS in Georgia found that pain relievers were the most commonly used drugs in the ME/CFS group. Sixty-five percent of patients with ME/CFS reported use of an NSAID and a narcotic pain reliever; this percentage was significantly greater than the use of pain relievers by subjects designated as having insufficient symptoms to diagnose as ME/CFS and control subjects.[22] The drugs surveyed by Boneva et al[22] included acetaminophen and NSAIDs such as ibuprofen, and aspirin, while specific drugs in the narcotic category were not specified. Opiates and opioids sometimes prescribed to treat the hyperalgesia and chronic pain associated with CFS/fibromyalgia have been found to be only minimally effective,[23] although large-scale studies specific to ME/CFS have not yet been performed.

NSAIDs are classified as either general or specific inhibitors of cyclooxygenase (COX)-2.[24] Nonspecific NSAIDs are commonly available over the counter and include pain relievers such as aspirin and ibuprofen. Although acetaminophen is not an NSAID, it is included in this category because its mode of action—the inhibition of the COX 1 and 2 enzymes—is the same as that of nonspecific NSAIDs.[25] While NSAIDs do target the mechanisms by which oxidative stress–inducing prostaglandin derivatives form, these same derivatives have been shown to form independent of the function of COX enzymes.[26,27] Therefore, nonspecific NSAIDs are most useful as symptom-relief agents.

On the other hand, the subclass of NSAIDs consisting of COX-2–specific inhibitors are of potential interest in treating ME/CFS because it has been demonstrated that COX-2 plays a central role in the replication of viruses and is up-regulated during viral infection.[28,29] If ME/CFS does in fact have a viral origin, selective COX-2 inhibitors may be useful in treating latent infections. Selective COX-2 inhibitors, such as celecoxib, have been demonstrated to be effective in the treatment of fibromyalgia.[29] Although fibromyalgia is believed to be a distinct condition, symptoms often overlap with those of ME/CFS.[30] If further research demonstrates a link between the etiologies of the 2 conditions, there may be cause for the use of drugs such as celecoxib in a subset of patients with ME/CFS. Furthermore, these specific inhibitors target COX-2, an enzyme driving inflammation and pain, without targeting COX-1, the inhibition of which has been

associated with gastrointestinal distress.[31] While the reduction of off-target effects is a goal of most drug-development efforts, minimizing side effects is especially important in patients with ME/CFS who already experience a wide variety of comorbidities, often including gastrointestinal disorders such as irritable bowel syndrome.[32]

Currently, there is a lack of clinical research focusing on the use of specific COX-2 inhibitors in the treatment of ME/CFS. While it is apparent and expected that NSAIDs are being used to mitigate pain in patients with ME/CFS, it may be warranted to further expand research into the efficacy of COX-2−specific inhibitors in particular. First, however, it may be necessary to establish a viral etiology for ME/CFS and, if such a cause exists, to identify biomarkers of the corresponding subpopulation. Unfortunately, at this point in time, research supporting a broader use of antivirals and a viral etiology remains inconclusive.

Antidepressants

The use of antidepressants in the treatment of ME/CFS has a multifaceted basis. In many cases, it is unclear whether depressive symptoms associated with ME/CFS are direct symptoms of the disease or are a secondary effect, brought on by the psychological pressure of living with a debilitating illness.[6,33,34] Due to the heterogeneous nature of the disease, it is possible that either or both of these may be the cause of depressive symptoms. Although arguments regarding the role of depression in ME/CFS persist, the treatment of depressive symptoms is still a necessary priority. Furthermore, energy production and mitochondrial dysfunction are believed to possibly play a role in ME/CFS. Some antidepressants, such as MAO inhibitors, operate by targeting mitochondrial enzymes.[35] Therefore, in addition to providing direct symptom relief in patients with ME/CFS, antidepressants may address the underlying molecular mechanisms of illness.

Although there have been a limited number of studies on the efficacy of antidepressants in treating ME/CFS, the findings have again been largely inconclusive and contradictory. A randomized, double-blind study on the effectiveness of the tricyclic MAO inhibitor fluoxetine in 96 participants found that a daily dosage of fluoxetine had no beneficial effect on the symptoms of ME/CFS.[36] Neither depressed nor nondepressed patients with ME/CFS showed significant improvement, leading the investigators to conclude that depressive symptoms seen in ME/CFS may arise from unique mechanisms not shared by other depressive disorders.[36] An open-label study of moclobemide, another MAO inhibitor, in 49 patients with ME/CFS found "significant but small reductions in fatigue, depression, anxiety and somatic amplification, as well as a modest overall improvement" (Pg. 47 please)[37] in patients, indicating that this class of drugs may be of interest. However, the investigators noted that further, double-blind, placebo-controlled studies are necessary to confirm these findings. A 2003 study of the selective serotonin and norepinephrine reuptake inhibitor venlafaxine in fibromyalgia found significant improvements in pain, fatigue, and depressive symptoms.[38] However, the relevance of the study is questionable, as fibromyalgia and ME/CFS are distinct clinical entities despite sharing similar symptom profiles, and only a total of 15 participants were enrolled. A 2008 study on the effectiveness of escitalopram, a selective serotonin reuptake inhibitor, found significant reductions in the symptomatic presentation of both ME/CFS and depressive symptoms.[39] However, this study was neither double blinded nor placebo controlled, and the study population comprised only 16 individuals in total.

As with antiviral drug trials, studies of antidepressant treatments in patients with ME/CFS may lack statistical power and rigorous study design. While some of these trials appear to show promise, there has thus far been either insufficient ability or interest to further explore these antidepressant treatments in double-blinded, placebo-controlled studies. However, if true depressive disorders can be diagnosed comorbidly with ME/CFS, antidepressants may be of use in delivering improvements in quality of life. Until such studies are undertaken, it is difficult to determine the true effectiveness of antidepressants in patients with ME/CFS.

Other treatments

There is a growing body of literature on treatments for ME/CFS that do not fall into either of the above categories and that are not well developed enough to garner their own category. A 1998 randomized, controlled study by McKenzie et al[40] tested the effect of hydrocortisone application in a cohort of 70 patients with ME/CFS. The basis for this study was that researchers had found dysregulation of the

hypothalamic–pituitary adrenal axis in some patients with ME/CFS, and thus it was believed that hormone supplementation may be beneficial.[41] However, the results did not show a statistically significant improvement in patients with ME/CFS receiving hydrocortisone compared to control subjects. Another study, conducted by Steinberg et al[42] in 1996, tested oral dosages of terfenadine, an antihistamine, in 30 patients with ME/CFS in a placebo-controlled manner, but found no evidence of improvement in any patients. A 2014 study of coenzyme Q and NADH supplementation in 73 patients with ME/CFS was attempted based on evidence of decreased energy production via depleted coenzyme Q and ATP levels, and decreased mitochondrial function in ME/CFS.[43,44] This study found significantly increased levels of the supplemented coenzymes after treatment, as well as increased ATP and citrate synthase levels and a decrease in lipid peroxidation. However, these changes corresponded to only a small improvement in symptom presentation versus placebo in 1 of 4 categories assessed, this being the Fatigue Impact Scale total score.[44] Since various studies have found evidence of B-cell dysfunction in ME/CFS,[45–47] the B cell–depleting anti-CD20 antibody rituximab has also attracted interest. While a 2015 trial found positive responses in approximately two thirds of 28 patients,[48] this finding has not been replicated by other groups,[49] and the mechanism of action of rituximab in this context is unclear.[50] Thus, none of these treatments targeting anecdotally dysregulated pathways individually in patients with ME/CFS have so far shown significant and broad benefit. These findings reaffirm that the heterogeneous nature of ME/CFS presents important challenges to both the identification of illness mechanisms and the development of treatments that will reliably benefit a significant number of these patients. Moreover, these findings also raise the issue of robustness in biological networks and regulatory stability. Theoretical work by our group has suggested that recalibration of endocrine–immune regulation may be involved in supporting the persistence of ME/CFS and may be involved at least in part in its resistance to single-agent interventions.[51]

DISCUSSION

The current literature on the treatment of ME/CFS leans strongly toward a single conclusion—that there is no single solution. The assumption that a single drug can successfully treat ME/CFS is likely incorrect. The multifaceted, complex nature of ME/CFS may instead be more effectively treated with combination therapies, tailored to the specific causes and symptoms present in each individual patient. These potential therapies will be supported by advancements in 2 fields. First, advancements in systems biology and systems-level analysis of the biological drivers behind ME/CFS will more clearly inform researchers as to which illness mechanisms are viable targets for treatment.[3,52] Systems biology approaches have already been undertaken to analyze gene coexpression networks, perform pathway analysis, and explore metabolic pathway perturbations in ME/CFS.[53–55] Generating robust tools for system-wide analysis of ME/CFS, at all of the conventional "-omics" levels, may prove invaluable for the discovery of a treatment or cure.

While systems biology approaches are needed to conduct basic research into the underlying causes of ME/CFS, personalized medicine and translational medicine are the necessary complements to such research. Personalized or precision medicine is a field that seeks to tailor treatments to individuals or narrow groups of individuals based on genetic or epigenetic makeup as well as a variety of other nongeneralizable patient characteristics.[56] It has been promoted by some as the future of medicine, and it may prove invaluable in treating patients with ME/CFS, who abound with nongeneralizable characteristics. Although it is currently difficult to conduct focused such research in ME/CFS, due primarily to the scarcity of promising pharmaceutical agents and poorly understood disease underpinnings, advances in personalized strategies will no doubt play a role in the future of ME/CFS treatment. Since, with the possible exception of rintatolimod, existing drugs have largely failed, research into new treatment paradigms is called for, and must be developed with an eye for translation. As researchers gain a greater understanding of the etiology and progression of ME/CFS, modern approaches using multidrug, tailored interventions may take the place of conventional single-drug approaches when combined with targeted research into new pharmacologic targets and compounds. The combination of treatment-responsive subtyping together with the design of combination therapies could well prove to be at least one solution

to the current stalemate and may help to turn the tables in ME/CFS, an illness that has for so long been considered largely incurable.

CONCLUSIONS

The heterogeneous nature of ME/CFS in symptoms profiles and perhaps in etiology remain a significant challenge in the search for effective drugs and the design of insightful clinical trials supported by optimal inclusion criteria. Clinical trials conducted so far have been of generally poor design and hampered by a lack of statistical power and a confluence of confounding factors. There is a great need for larger-scale, longitudinal studies focused on a more clearly defined subset of ME/CFS as well as a greater consideration of potential synergies between interventions and the suitability of combination therapies. Without such studies, many promising treatments will remain just that—promising—but lacking enough evidence to support their widespread adoption.

Conflicts of interest

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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REFERENCES

1. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med*. 1994;121(12):953–959. https://doi.org/10.7326/0003-4819-121-12-199412150-00009.
2. Sharif K, Watad A, Bragazzi NL, et al. On chronic fatigue syndrome and nosological categories. *Clin Rheumatol*. 2018;37:1161–1170. https://doi.org/10.1007/s10067-018-4009-2.
3. Broderick G, Katz BZ, Fernandes H, et al. Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue. *J Transl Med*. 2012;10:191. https://doi.org/10.1186/1479-5876-10-191.
4. Blomberg J, Gottfries C-G, Elfaitouri A, Rizwan M, Rosén A. Infection elicited autoimmunity and myalgic encephalomyelitis/chronic fatigue syndrome: an explanatory model. *Front Immunol*. 2018;9:229. https://doi.org/10.3389/fimmu.2018.00229.
5. Nagy-Szakal D, Barupal DK, Lee B, et al. Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics. *Sci Rep*. 2018;8:10056. https://doi.org/10.1038/s41598-018-28477-9.
6. Morris G, Maes M. A neuro-immune model of myalgic encephalomyelitis/chronic fatigue syndrome. *Metab Brain Dis*. 2013;28:523–540. https://doi.org/10.1007/s11011-012-9324-8.
7. Keenan PA. Brain MRI abnormalities exist in chronic fatigue syndrome. *J Neurol Sci*. 1999;171:1–2.
8. Wostyn P, De Deyn PP. The putative glymphatic signature of chronic fatigue syndrome: a new view on the disease pathogenesis and therapy. *Med Hypotheses*. 2018;118:142–145. https://doi.org/10.1016/j.mehy.2018.07.007.
9. Morris G, Berk M, Walder K, Maes M. The Putative Role of Viruses, Bacteria, and Chronic Fungal Biotoxin Exposure in the Genesis of Intractable Fatigue Accompanied by Cognitive and Physical Disability. *Mol Neurobiol*. 2016 May;53(4):2550–2571. https://doi.org/10.1007/s12035-015-9262-7. Epub 2015 Jun 17.
10. Maclachlan L, Watson S, Gallagher P, et al. Are current chronic fatigue syndrome criteria diagnosing different disease phenotypes? *PLoS One*. 2017;12, e0186885. https://doi.org/10.1371/journal.pone.0186885.
11. Twisk FNM, Maes M. A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS. *Neuro Endocrinol Lett*. 2009;30:284–299.
12. Chia J, Chia A, Voeller M, Lee T, Chang R. Acute enterovirus infection followed by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and viral persistence. *J Clin Pathol*. 2010;63:165–168. https://doi.org/10.1136/jcp.2009.070466.
13. Jason LA, Katz BZ, Shiraishi Y, Mears CJ, Im Y, Taylor RR. Predictors of post-infectious chronic fatigue syndrome in adolescents. *Health Psychol Behav Med*. 2014;2:41–51. https://doi.org/10.1080/21642850.2013.869176.
14. Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. *N Engl J Med*. 1988;319:1692–1698. https://doi.org/10.1056/NEJM198812293192602.

15. Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up. *In Vivo*. 2007;21:707–713.
16. Montoya JG, Kogelnik AM, Bhangoo M, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. *J Med Virol*. 2013;85:2101–2109. https://doi.org/10.1002/jmv.23713.
17. Kogelnik AM, Loomis K, Hoegh-Petersen M, Rosso F, Hischier C, Montoya JG. Use of valganciclovir in patients with elevated antibody titers against human herpesvirus-6 (HHV-6) and Epstein-Barr virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue. *J Clin Virol*. 2006;3(suppl 7):S33–S38. https://doi.org/10.1016/S1386-653270009-9.
18. Mitchell WM. Efficacy of rintatolimod in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *Expert Rev Clin Pharmacol*. 2016;9:755–770. https://doi.org/10.1586/17512433.2016.1172960.
19. Hemispherx Biopharma Inc. Product Candidates. Available at: https://www.hemispherx.net/product-candidates-overview.php. Accessed December 2, 2018.
20. Strayer DR, Carter W, Strauss KI, et al. Long term improvements in patients with chronic fatigue syndrome treated with Ampligen. *J Chronic Fatigue Syndr*. 1995;1:35–53. https://doi.org/10.1300/J092v01n01_04.
21. Strayer DR, Carter WA, Stouch BC, et al. A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. *PLoS One*. 2012;7, e31334. https://doi.org/10.1371/journal.pone.0031334.
22. Boneva RS, Lin J-MS, Maloney EM, Jones JF, Reeves WC. Use of medications by people with chronic fatigue syndrome and healthy persons: a population-based study of fatiguing illness in Georgia. *Health Qual Life Outcomes*. 2009;7:67. https://doi.org/10.1186/1477-7525-7-67.
23. Hermans L, Nijs J, Calders P, et al. Influence of morphine and naloxone on pain modulation in rheumatoid arthritis, chronic fatigue syndrome/fibromyalgia, and controls: a double-blind, randomized, placebo-controlled, cross-over study. *Pain Pract Off J World Inst Pain*. 2018;18:418–430. https://doi.org/10.1111/papr.12613.
24. Ong CKS, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. *Clin Med Res*. 2007;5:19–34. https://doi.org/10.3121/cmr.2007.698.
25. Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. *FASEB J Off Publ Fed Am Soc Exp Biol*. 2008;22:383–390. https://doi.org/10.1096/fj.07-8506com.
26. Morrow JD, Harris TM, Jackson Roberts L. Noncyclooxygenase oxidative formation of a series of novel prostaglandins: analytical ramifications for measurement of eicosanoids. *Anal Biochem*. 1990;184:1–10. https://doi.org/10.1016/0003-269790002-Q.
27. Morris G, Maes M. Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. *BMC Med*. 2013;11:205. https://doi.org/10.1186/1741-7015-11-205.
28. Steer SA, Corbett JA. The role and regulation of COX-2 during viral infection. *Viral Immunol*. 2003;16:447–460. https://doi.org/10.1089/088282403771926283.
29. Pridgen WL, Duffy C, Gendreau JF, Gendreau RM. A famciclovir + celecoxib combination treatment is safe and efficacious in the treatment of fibromyalgia. *J Pain Res*. 2017;10:451–460. https://doi.org/10.2147/JPR.S127288.
30. Abbi B, Natelson BH. Is chronic fatigue syndrome the same illness as fibromyalgia: evaluating the 'single syndrome' hypothesis. *QJM Int J Med*. 2013;106:3–9. https://doi.org/10.1093/qjmed/hcs156.
31. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *Br Med J*. 2006;332:1302–1308.
32. Lakhan SE, Kirchgessner A. Gut inflammation in chronic fatigue syndrome. *Nutr Metab*. 2010;7:79. https://doi.org/10.1186/1743-7075-7-79.
33. Lynch S, Seth R, Montgomery S. Antidepressant therapy in the chronic fatigue syndrome. *Br J Gen Pract*. 1991;41:339–342.
34. Castro-Marrero J, Sáez-Francàs N, Santillo D, Alegre J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome: therapy and management in CFS/ME. *Br J Pharmacol*. 2017;174:345–369. https://doi.org/10.1111/bph.13702.
35. Fiedorowicz JG, Swartz KL. The role of monoamine oxidase inhibitors in current psychiatric practice. *J Psychiatr Pract*. 2004;10(4):239–248.
36. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet Lond Engl*. 1996;347(9005):858–861.
37. White PD, Cleary KJ. An open study of the efficacy and adverse effects of moclobemide in patients with the

chronic fatigue syndrome. *Int Clin Psychopharmacol*. 1997;12:47–52.
38. Sayar K, Aksu G, Ak I, Tosun M. Venlafaxine treatment of fibromyalgia. *Ann Pharmacother*. 2003;37:1561–1565. https://doi.org/10.1345/aph.1D112.
39. Amsterdam JD, Shults J, Rutherford N. Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:100–106. https://doi.org/10.1016/j.pnpbp.2007.07.019.
40. McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. *JAMA*. 1998;280:1061–1066. https://doi.org/10.1001/jama.280.12.1061.
41. Demitrack MA, Dale JK, Straus SE, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab*. 1991;73:1224–1234. https://doi.org/10.1210/jcem-73-6-1224.
42. Steinberg P, McNutt BE, Marshall P, et al. Double-blind placebo-controlled study of the efficacy of oral terfenadine in the treatment of chronic fatigue syndrome. *J Allergy Clin Immunol*. 1996;97:119–126. https://doi.org/10.1016/S0091-674970290-7.
43. Castro-Marrero J, Cordero MD, Sáez-Francas N, et al. Could mitochondrial dysfunction be a differentiating marker between chronic fatigue syndrome and fibromyalgia? *Antioxid Redox Signal*. 2013;19:1855–1860. https://doi.org/10.1089/ars.2013.5346.
44. Castro-Marrero J, Cordero MD, Segundo MJ, et al. Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome? *Antioxid Redox Signal*. 2014;22:679–685. https://doi.org/10.1089/ars.2014.6181.
45. Nguyen CB, Alsøe L, Lindvall JM, et al. Whole blood gene expression in adolescent chronic fatigue syndrome: an exploratory cross-sectional study suggesting altered B cell differentiation and survival. *J Transl Med*. 2017;15:102. https://doi.org/10.1186/s12967-017-1201-0.
46. Loebel M, Strohschein K, Giannini C, et al. Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. *PLoS One*. 2014;9, e85387. https://doi.org/10.1371/journal.pone.0085387.
47. Mensah F, Bansal A, Berkovitz S, et al. Extended B cell phenotype in patients with myalgic encephalomyelitis/chronic fatigue syndrome: a cross-sectional study. *Clin Exp Immunol*. 2016;184:237–247. https://doi.org/10.1111/cei.12749.
48. Fluge Ø, Risa K, Lunde S, et al. B-lymphocyte depletion in myalgic encephalopathy/chronic fatigue syndrome. An open-label phase II study with rituximab maintenance treatment. *PLoS One*. 2015;10, e0129898. https://doi.org/10.1371/journal.pone.0129898.
49. Wyller VB, Reme SE, Mollnes TE. Chronic fatigue syndrome/myalgic encephalo-myelitis–pathophysiology, diagnosis and treatment. *Tidsskr Den Nor Laegeforening Tidsskr Prakt Med Ny Raekke*. 2015;135:2172–2175. https://doi.org/10.4045/tidsskr.15.1180.
50. Lunde S, Kristoffersen EK, Sapkota D, et al. Serum BAFF and APRIL levels, T-lymphocyte subsets, and immunoglobulins after B-cell depletion using the monoclonal anti-CD20 antibody rituximab in myalgic encephalopathy/chronic fatigue syndrome. *PLoS One*. 2016;11, e0161226. https://doi.org/10.1371/journal.pone.0161226.
51. Craddock TJ, Fritsch P, Rice MA, et al. A role for homeostatic drive in the perpetuation of complex chronic illness: gulf War illness and chronic fatigue syndrome. *PLoS One*. 2014;9, e84839. https://doi.org/10.1371/journal.pone.0084839.
52. Smylie AL, Broderick G, Fernandes H, et al. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. *BMC Immunol*. 2013;14:29. https://doi.org/10.1186/1471-2172-14-29.
53. Emmert-Streib F. The chronic fatigue syndrome: a comparative pathway analysis. *J Comput Biol*. 2007;14:961–972. https://doi.org/10.1089/cmb.2007.0041.
54. Presson AP, Sobel EM, Papp JC, et al. Integrated weighted gene co-expression network analysis with an application to chronic fatigue syndrome. *BMC Syst Biol*. 2008;2:95. https://doi.org/10.1186/1752-0509-2-95.
55. Naviaux RK, Naviaux JC, Li K, et al. Metabolic features of chronic fatigue syndrome. *Proc Natl Acad Sci*. 2016;113:E5472–E5480. https://doi.org/10.1073/pnas.1607571113.
56. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010;363:301–304. https://doi.org/10.1056/NEJMp1006304.

Address correspondence to: Gordon Broderick, Ph.D., Medical Office Building, Room 590, Rochester General Hospital, 1425 Portland Avenue, Rochester, NY 14621, USA. E-mail: gordon.broderick@rochesterregional.org