Are complex therapies required as pharmacological treatments of fibromyalgia?

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Sheffield Hallam University, Biomedical Research Centre, Faculty of Health and Wellbeing, City Campus, Sheffield S1 1WB, UK Tel.: +44 114 225 3057; Fax: +44 114 225 3066; k.lawson@shu.ac.uk Fibromyalgia (FM), a chronic pain condition with many auxiliary symptoms and co-morbidities, is estimated to affect 2-4% of the general population. Current management involves medications that remain largely empiric, which many patients may find either insufficient to control their symptoms or difficult to tolerate. The lack of a complete understanding of the pathophysiological processes underlying this condition limits the ability to provide rationally designed, mechanistically based treatments. As a consequence, treatment is often directed towards individual symptoms rather than management of the condition. This has resulted in limited success of clinical trials in FM, which may be related to an apparent reductionist approach to their design for the evaluation of a complex condition. The complexity of FM suggests that, to date, monotherapy will not adequately address the condition.

Fibromyalgia (FM) is a chronic pain condition in which patients experience many auxiliary symptoms, such as sleep disturbances and chronic fatigue [1-3]. It is estimated to affect 2-4% of the general population, increasing to greater than 7% of those over 70 years of age. The management of FM is complicated by the lack of a universally accepted pathophysiological mechanism and overlap with symptoms of other health conditions (e.g., chronic fatigue syndrome and myofascial pain). A number of hypotheses have been suggested regarding the pathophysiology of FM, including a dysfunction of pain modulatory systems within the CNS, neuroendocrine dysfunction and dysautonomia (disruption in the sympathetic autonomic nervous system) [4-6]. The cause of the interference in pain processing remains unclear, although involvement of chronic psychological stressors, peripheral pain generators and inflammatory mediators has been proposed [7]. Although pain is a predominant feature of FM, alteration in pain processing does not, however, explain other commonly experienced symptoms such as fatigue and sleep disturbances.

Current drug treatment

Current pharmacological treatment (Box 1) remains largely empiric, with a variety of drugs being used to treat the condition through the management of individual symptoms [8–11]. Many patients with FM may find current medications either insufficient to control their symptoms or difficult to tolerate. The latter is compounded by these patients demonstrating an apparent high sensitivity to adverse effects of drugs. The management of FM is further complicated by the lack of formal evidence-based medicine treatment guidelines, although recommendations are starting to emerge (e.g., EULAR recommendations) [12]. As a consequence of these factors, the majority of FM patients only obtain modest relief to drug treatments and general compliance is low.

REVIEW

Bioamine modulators

First-line pharmacological therapies for FM are often low-dose antidepressants, particularly tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs). Clinical trials have demonstrated that TCAs and SNRIs have proven benefits related to reduction of the pain and fatigue associated with FM, however the greatest effect of the former group of drugs was improved sleep quality [8-11,13-16]. SSRIs, however, have yielded mixed results in clinical trials with FM patients [11]. These findings are supportive of the relief of pain associated with FM requiring modulation of both norepinephrine and serotonin levels as obtained with the TCAs and SNRIs. Although antidepressants are often the mainstay treatment of FM, TCAs in particular are not well tolerated by patients, present with unpredictable responses and are not supported by long-term efficacy evidence. These limitations with TCAs as treatments appear to have been at least partially overcome by SNRIs [13-16].

Keywords: clinical trials, fatigue, fibromyalgia, pain, pharmacological treatments, sleep dysfunction



Box 1. Examples of current pharmacological treatments of fibromyalgia.

- Tricyclic antidepressants
 - Amitriptyline
 - Doxepin
- Serotonin-norepinephrine reuptake inhibitors
 - Duloxetine
 - Milnacipran
 - Venlafaxine
- Selective serotonin reuptake inhibitors
 - Fluoxetine
 - Citalopram
- Dopamine agonist
- Pamipexole
- Anti-epileptics
- Pregabalin
 Gabapentin
- Sedative hypnotics
 - Benzodiazepines
 - Zopiclone
 - Zolpidem
 - Sodium oxybate
- Muscle relaxants
- Tizanidine
- Cyclobenzaprine
- Analgesics
- Dihydrocodeine
- Morphine
- Tramadol
- Paracetamol (acetaminophen)

The dopamine D3/D2 receptor agonist, pramipexole, reduced pain and improved fatigue and overall function in patients with FM [17]. These findings are consistent with the disruption of dopaminergic neurotransmission and an abnormal dopamine response to pain observed in patients with FM [18,19]. Interestingly, sibutramine, a serotonin/noradrenaline/dopamine reuptake inhibitor, has also been reported to improve pain, sleep and fatigue in patients with FM in a pilot retrospective study [20].

Analgesics

Although opioid analgesics are frequently used to treat chronic pain conditions, their use in the treatment of FM remains controversial because of a lack of evidence in this patient population and the potential of long-term use leading to tolerance and dependence. Opioid analgesics may be introduced when severe symptoms are unresponsive to other medications, with use usually on an as-needed basis or for short periods of time. Tramadol, classified as a non-narcotic analgesic, has demonstrated efficacy in FM clinical trials [21]. Acetaminophen (paracetamol) is prescribed in Europe for patients with FM, although there is no efficacy evidence to support use in this patient population. In addition, there is no evidence that nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen) are effective in the treatment of FM, although studies have indicated that patients express a statistically significant preference for NSAIDs compared with acetaminophen [22].

Sedative hypnotics

Patients with FM experience disrupted or nonrestorative sleep, conditions that benefit from treatment with sedative hypnotics, such as benzodiazepines and the newer agents zolpidem and zopiclone [23-24]. These drugs do not, however, modify the pain symptoms associated with FM, supporting the debate regarding the role of the sleep disturbance in the pathogenesis of this condition. Thus, sedative hypnotics as a monotherapy have limited use and are often prescribed on an as-needed basis for patients who do not gain sleep benefit from other treatments, such as antidepressants. By contrast, sodium oxybate provided significant improvements in the major symptoms of FM (i.e., pain, tenderness, sleep quality and fatigue) with a correlation (r = 0.55, p < 0.001) between changes in the pain scale and improvements in sleep quality, suggesting that the analgesic effect was related to improved sleep [25-26].

Anti-epileptic drugs

Anti-epileptic drugs (AEDs; e.g., gabapentin and pregabalin) can also be used to treat patients with FM. Efficacy evidence from clinical trials for AEDs in treating FM and other related pain syndromes is supportive of this approach [27–29]. Pregabalin and gabapentin have proved effective in reducing the pain and accompanying symptoms of FM, such as fatigue and sleep disturbance, while improving quality of life [27–29]. The effects of pregabalin were initiated within 1 week and maintained over a 6-month period, and the drug was well tolerated. The benefits offered by pregabalin have recently led to it being the first product to receive US FDA approval for FM.

Potential drug targets

Of the few drug therapies that have shown some value in this patient population, all are associated with limited efficacy and significant tolerability issues. The lack of universal success of a monotherapy approach supports the conclusion that either multiple targets may need to be involved in any drug treatment or the optimal target has not, as yet, been identified. The absence of understanding of the pathophysiological processes underlying this condition limits the ability to provide rationally designed, mechanistically based pharmacological treatment approaches. The efficacy of certain current drug treatments has been associated with increasing synaptic levels of bioaminergic neurotransmitters, particularly norepinephrine and serotonin, suggesting this mechanism may play a fundamental role in the therapy of FM [30,31]. Treatments that increase the activity of norepinephrine and serotonin may correct a deficit of neurotransmission in descending inhibitory pain pathways and, therefore, help reduce pain [32,33]. The evidence, however, does not support the notion that one of the bioamines is of greater importance, but suggests simultaneous modulation of all bioamines may be required. The limited efficacy of modulators of bioamine levels indicates that additional or other factors need to be targeted by pharmacological treatments. Pregabalin, the only FDAapproved treatment for FM, is believed to act at the $\alpha_2\delta_1$ subunit of voltage-gated calcium channels [34]. Data are awaited concerning the importance of this mechanism of action in the FM-patient population beyond that of the controlled environment of clinical trials.

Limitations for drug treatments

In addition to the very limited knowledge of the pathophysiology of FM, diagnosis and treatment are further complicated by the presence of the variety of pain and nonpain symptoms, and co-morbid conditions (Box 2) that can mask the underlying disorder. Thereby, misdiagnosis of the condition is common, often leading to inappropriate treatment. Furthermore, owing to a lack of universal guidelines for the treatment of FM, there is the potential of the various specialists (e.g., rheumatologists, psychiatrists and neurologists) to develop treatment regimens within their specific areas of interest and focus on particular symptoms rather than the condition as a whole. Many of the above factors will understandably be related to a low awareness of the condition amongst clinicians and healthcare professionals.

Most patients with FM require several drug therapies to treat their symptoms adequately, leading to expensive polypharmacy [12,35]. New drugs or newer formulations of older drugs (to improve their pharmacology) may not be

Box 2. Examples of conditions frequently co-morbid with fib<u>romyalgia</u>

- Chronic low back pain
- Irritable bowel syndrome
- Depression/anxiety
- Temporomandibular joint disorder
- Chronic fatigue syndrome
- Multiple chemical sensitivities
- Interstitial cystitis
- Rheumatoid arthritis
- Positional cervical myelopathy
- Chiari malformation

affordable to be included into the patient's drug regime and thereby may be withheld in favor of other, less expensive (generic) alternatives. These factors will hinder progress in understanding of the condition and development of more focused and effective therapies.

A number of drugs are currently in development for FM [30,31]. The current clinical activity in this area represents a major advance in interest by the pharmaceutical industry into this condition. This interest in FM and the recent approval by the FDA of pregabalin for the treatment of FM will provide much-needed validation for this debilitating condition. Regulatory body drug approvals should also lead, in addition to improved treatment, to improved diagnosis. For the majority of drugs in clinical trials for FM, however, this condition (and thereby the patient population) is secondary to other conditions for which the compound has been developed or approved. This circumstance is again a consequence of factors, such as the poor understanding of the pathophysiology of FM and difficulty in achieving good drug efficacy in such a heterogeneous patient population, which hinders the identification of viable drug targets.

Clinical trials for fibromyalgia

Many of the clinical trials of potential pharmacological treatments however have common limitations that influence the outcomes (Table 1). Pharmacological therapy of FM may take weeks before beneficial responses are observed across all symptoms with a need for long-term efficacy, therefore trials lasting a brief period may not achieve outcomes that are clinically applicable. It is pertinent to mention that in recent studies an improvement in pain was achieved within 1–2 weeks with pregabalin and duloxetine [16,27,29]. Although there is increasing evidence from clinical studies that certain pharmacological agents provide meaningful benefit in FM,

| Table 1. Limitations of | pharmacological treatment | t studies in fibromyalgia. |
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| Limitation | Action | Reason |
|---|--|--|
| Short duration | Efficacy data from longitudinal studies | FM is a chronic condition with fluctuating symptoms |
| Sample size (patient numbers) | Large studies including various co- morbidities | Heterogeneous patient population with co-morbidities and potential of more than one form of FM |
| Mean reduction in pain was primary outcome measure in many trials | Need to determine the proportion of patients who experience clinically important improvement | To enhance comparability and clinical applicability of trials |
| Lack of consensus of meaningful reduction in pain | Guidelines of standardized outcome measures of FM activity and improvement | To enhance comparability and clinical applicability of trials |
| Unclear whether improvement in pain intensity alone should define response to treatment | Guidelines of standardized outcome measures of FM activity and improvement | FM is a syndrome characterized by multiple symptoms in addition to pain |
| Inconsistent evaluation of associated symptoms (other than pain as the primary outcome) | Comprehensive evaluation of condition and symptoms | To enhance comparability and clinical applicability of trials |
| Use of dissimilar measures to assess symptoms and functional domains | Guidelines of standardized outcome measures of FM activity and improvement | To enhance comparability and clinical applicability of trials |
| Patients with co-morbid disorders often excluded | Systematic evaluation of patients with and without co-morbid disorders | Prognostic significance of co-morbidity and clinical applicability of trials |
| Most trials excluded patients with pain from some other disorder | Inclusion of patients with FM plus additional pain conditions | Potential triggers for the exacerbation of FM symptoms |
| Majority of subjects were women | Gender-specific studies | Although higher prevalence of FM in women, may not be generalizable to men |
| Investigation of single-treatment approach | Incorporate combination therapies | Many patients benefit from combination of pharmacological and nonpharmacological treatments |
| Current medications excluded | Concurrent drug therapy studies | Monotherapy not adequate and excluding current therapy can limit recruitment to trial, thus participants not representative of patient population |
| Placebo (inactive) control trials | Assessment of new therapy against active (current) comparator | Head-to-head comparison of treatments and ethical issues related to nontreatment (placebo) of subjects in trial design |

adequate proof of long-term efficacy is lacking. Clinical trials of appropriate duration are needed to provide sufficient time for the full impact of the treatment to be assessed. In a recent pharmacoeconomic evaluation of treatment for FM, of 58 trials studied, only 22 (38%) went beyond 3 months, and only seven (12%) extended to 12 months [35]. The longer trials involved nonpharmacological therapies. Furthermore, many of the 58 trials involved the use of relatively small patient numbers. Only six (10%) of the 58 trials studied had more than 100 patients and 16 (28%) trials had 50 or more patients in total. The outcomes of such studies are complicated by the heterogeneity of the patient population and proposals that there could be more than one form of FM [3,4]. Recent

randomized controlled trials have demonstrated durability of benefit (e.g., duloxetine studied over 12 months) in restricted cohorts (e.g., no males). Increase in the duration and cohort size of trials should not be solely to improve statistical significance for what is perhaps a weak therapy, but should provide a more realistic representation of the clinical situation. There is therefore a need for more naturalistic, larger studies, which include patients with various medical co-morbidities and involve concurrent therapies, in order to address the chronic nature of the condition and achieve better informed decisions between alternative treatments.

FM patients with co-morbidities, such as osteoarthritis or rheumatoid arthritis, which can be the norm rather than the exception in clinical practice, are often excluded from clinical trials. This exemplifies how a focus to simplify studies, because of the limited understanding of FM, will dictate the outcomes rather than the requirement of the condition. Full consideration of the issue of co-morbidities is beyond the scope of this article because of the extensive range of co-morbid conditions involved. Recent trials with antidepressants have, however, included FM patients with depression [14,15], a common co-morbidity, which represents a step forward in clinical trial design.

The primary focus of trials in FM has often been toward a single symptom end point, for example pain management, with marked efficacy being limited to subgroups of patients. The identification of treatment subgroups may be associated with differential symptom dominance in patient populations or biological subgrouping (where the pathological mechanisms are different although the symptoms are common). In addition, it is likely that many patients would benefit from combinations of pharmacological and nonpharmacological treatments [36], therefore when designing FM clinical trials a more realistic setting would ideally incorporate combination therapies.

Conclusion

FM is a complex condition, with pain the principal symptom and a number of other important domains involved, including fatigue and sleep disturbance, and is thus difficult to treat. The lack of understanding of the pathophysiology of FM has limited the availability of clues for the rational design of mechanistically based drug treatment approaches. This has been complicated by the heterogeneity of the FM patient population, hindering the development of a single set of guidelines for the treatment of FM. Current pharmacological treatment approaches have often been focused towards individual symptoms of FM and thereby prevented the identification of a single therapeutic approach. As a consequence, attempts to identify new therapies involve either the assessment of existing therapeutic strategies with the potential of improving tolerability, or evaluation of drugs that have previously demonstrated efficacy in another condition for a symptom associated with FM. The complexities of FM, however, have limited the success of many of the clinical trials. Design of future trials, with an adaptive approach, needs to incorporate many factors to

ensure clinical applicability of the outcomes. Interestingly, the core domains to be recommended for assessment in FM studies identified by clinician-investigators were not fully concordant with those identified by patients as most important [37]. The clinician-investigators may have been influenced by practicality of assessment of the domains rather than just relevance to the condition. The management of patients with FM requires an individualized treatment approach taking into consideration the FM symptoms and their severity and the presence of co-morbidities. Well-controlled clinical trials to test the efficacy of therapies will help to identify which patient groups might benefit from a particular treatment. Positive outcomes from these trials will enhance the opportunity of a drug receiving regulatory approval for the management of FM and should provide insight into the biology of this condition, yielding potential clues for the development of more specific drugs.

Future perspective

A greater understanding of FM, gained from the development and use of focused therapies, will lead to a more representative design in clinical trials. Monotherapy randomized placebo-controlled clinical trials in FM have only enabled identification of marginal improvements in the clinical state. The development of flexible or adaptive design will enable trials to be more representative for the patient population with this complex condition (i.e., several fluctuating symptom domains, various co-morbidities) with the necessity of multitherapy approaches. The official recognition of pharmacological therapies for FM will form the basis for treatment guidelines that can be universally adopted. The success of such therapies will give clues to the biology associated with FM and thus lead to the development of more robust and universally accepted diagnostic tools. Improved diagnosis in combination with the development of condition, rather than symptom-focused therapies, will lead to further advancement in clinical trial design.

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Executive summary

Current drug treatment

- A wide variety of drugs are used for the management of individual symptoms as treatment of fibromyalgia.
- Many patients with fibromyalgia find current medications either insufficient to control their symptoms or difficult to tolerate.

Potential drug targets

- The absence of understanding of the pathophysiology underlying this condition limits the ability to provide rationally designed, mechanistically based pharmacological treatment approaches.
- The lack of universal success of a monotherapy approach reveals the need for action on multiple drug targets to achieve clinically acceptable efficacy in the total patient population.

Limitations for drug treatments

- In addition to the management of pain and auxiliary symptoms, treatment of fibromyalgia is complicated by the presence of co-morbidities.
- Guidelines for the treatment of fibromyalgia are emerging (European League Against Rheumatism recommendations), but are not yet universally accepted.

Clinical trials for fibromyalgia

- Many clinical trials of fibromyalgia have limitations that prevent outcomes achieving clinical applicability.
- There is a need for more naturalistic, larger long-term efficacy studies that include patients with various medical co-morbidities and on other fibromyalgia medications.

Conclusion

- Treatment approaches taking into consideration the profile of symptoms and the presence of co-morbidities are required.
- Development of drugs focused towards patient subsets will provide essential clues to the differing pathophysiological processes within this heterogeneous population.

Future perspective

- Development of flexible or adaptive design will enable trials to be more representative for the patient population with this complex condition (i.e., several fluctuating symptom domains and various co-morbidities) with the necessity of multitherapy approaches.
- Improved diagnosis in combination with the development of condition, rather than symptom-focused therapies, will lead to further advancement in clinical trial design.

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