CME

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Fibromyalgia

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Most doctors—particularly rheumatologists, pain specialists, and general practitioners—are familiar with patients who describe chronic pain all over the body, which is associated with a range of other symptoms including poor sleep, fatigue, and depression. This complex of symptoms is sometimes referred to as fibromyalgia. Management of patients with this condition is often complex and challenging. The diagnosis of fibromyalgia has long been controversial, with some experts questioning whether it exists as a separate entity.[1] However, the symptoms and distress experienced by patients with fibromyalgia are real. The causes of fibromyalgia are incompletely understood, and optimal management is compromised by the limited evidence base for the available treatments. This article reviews current thinking about what fibromyalgia is, whether it is a useful diagnosis to make, and which drugs and non-drug treatments can be used to treat it.

What is fibromyalgia and how common is it?

In general medical practice, fibromyalgia is diagnosed in patients with chronic widespread pain and multiple muscular tender points on examination or associated symptoms of fatigue, unrefreshing sleep, or cognitive dysfunction (or a combination thereof). Many patients have both tender points and associated symptoms.

Chronic widespread pain is defined in epidemiological studies as pain for at least three months, affecting both sides of the body, both above and below the waist.[2 3] Epidemiological evidence from several countries shows that it is a common problem, present in about 10% of the population.[3 4] Not all of these people have fibromyalgia. The population prevalence of fibromyalgia was first measured as about 2% using consensus classification criteria for fibromyalgia published by the American College of Rheumatology (ACR) in 1990.[2-5] These criteria (sensitivity 88.4%, specificity 81.1%) were simple—fibromyalgia could be diagnosed in a patient with chronic widespread pain if at least 11 of 18 specific sites on the body surface were tender to digital palpation. However, the tender point test is hard to standardise, some healthy people also have tender points, and these criteria take no account of a history of symptoms commonly seen in fibromyalgia, such as sleep disturbance and tiredness.

For the general clinician, alternative criteria produced by the ACR in 2010 may be more useful. These criteria do not require palpation of tender points. Instead patients are assessed by the widespread pain index—which divides the body into 19 regions and scores how many regions are reported as painful—and a symptom severity score that assesses severity of fatigue, unrefreshing sleep, and cognitive symptoms. The widespread pain index and symptom severity scores have been combined into a single questionnaire with a maximum score of 31,[6 7] which can be completed by self report. Two recently published population surveys using this 31 point questionnaire found a population prevalence for fibromyalgia of 2.1% in Germany[8] and 6.4% in Minnesota, USA.[7] In the German study, a cut-off questionnaire score of 12-13 was statistically best at distinguishing those who fulfilled the ACR 2010 criteria from those who did not, but there was no sharp division of clinical features between populations above and below this score.[8] The authors concluded that patients with fibromyalgia are not a separate discrete group but instead constitute the upper end of a continuous spectrum of polysymptomatic distress within the population.[8]

Figure 1 summarises the way in which clinical features can be used to diagnose fibromyalgia by general clinicians or specialists.

Who gets fibromyalgia?

Fibromyalgia has often been considered to affect mostly women. The Minnesota population survey found that 7.7% of women and 4.9% of men fulfilled ACR 2010 criteria for fibromyalgia, but a parallel medical records study in the same population found that only 27% of these people had been diagnosed with the condition.[7] Strikingly, the prevalence of medically diagnosed fibromyalgia was 2% in women but only 0.15% in men, a difference inconsistent with the true population prevalence figures.[7] Similarly, although most patients diagnosed in clinics are young or middle aged, population surveys show clearly that the prevalence rises steadily with age, with a maximum prevalence in the over 60s.[3 7] Perhaps older people with chronic widespread pain are diagnosed with osteoarthritis rather

SUMMARY POINTS

- Symptoms of fibromyalgia are chronic widespread pain associated with unrefreshing sleep and tiredness
- Fibromyalgia is not a diagnosis of exclusion and often occurs in patients with other conditions, such as inflammatory arthritis and osteoarthritis
- No clear pathophysiological mechanism for fibromyalgia has been established, but evidence suggests that there is an abnormality in central pain processing
- Diagnosing fibromyalgia can allow the patient's polysymptomatic distress to be explained, thereby reducing fear and doubt
- Fibromyalgia has no cure, but a range of drug and non-drug treatments can reduce symptoms and their impact on the patient's life
- Trial evidence for all forms of treatment in fibromyalgia generally shows only small to moderate average effects

SOURCES AND SELECTION CRITERIA

We used recommendations from three current guidelines: those from the Canadian Pain Society, the Association of Scientific Medical Societies in Germany (AWMF, 2012; English version www.awmf.org/leitlinien/detail/ll/041-004.html), and the European League Against Rheumatism (EULAR, 2008). These were supplemented by data from current Cochrane reviews and a PubMed search for systematic reviews of drug treatment for fibromyalgia. We focused on drugs with a licence for use in the treatment of fibromyalgia in one or more major jurisdiction or drugs that are in widespread use for other indications.

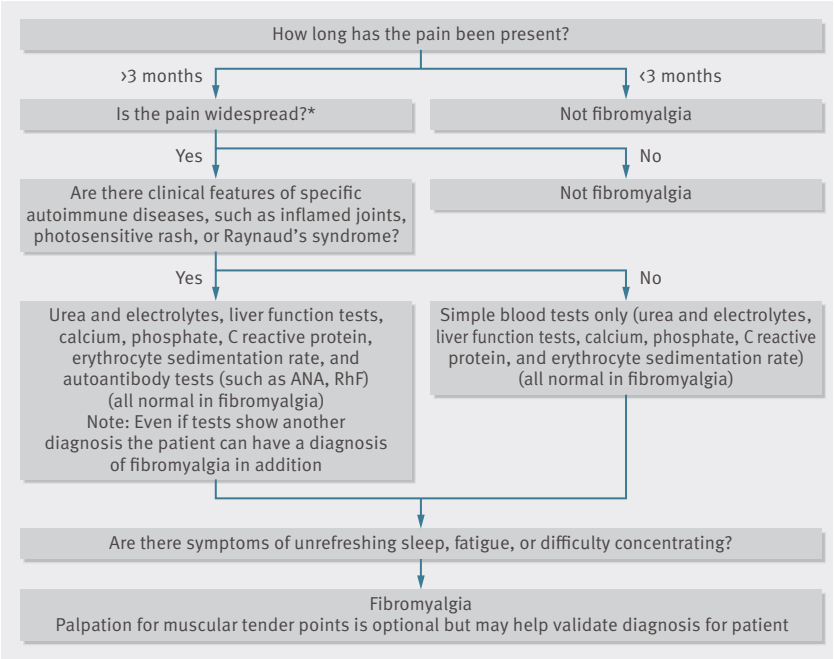

Fig 1 | Flow chart for diagnosis of fibromyalgia. ANA=antinuclear antibodies; RhF=rheumatoid factor. *Widespread pain defined as pain both above and below the waist and on both sides of the body

than fibromyalgia. Fibromyalgia is not restricted to developed countries. A large study in Bangladesh (n=5211) involving door-to-door surveys with a 99% response rate found fibromyalgia (ACR 1990 criteria) in 4.4% of people in a rural village, 3.2% in a poor city area, and 3.3% in a wealthy urban area.[5] These figures are similar to those seen in Western countries using the same diagnostic criteria.[3 7]

What causes fibromyalgia?

We do not know exactly what causes fibromyalgia. Patients have no consistent structural or functional abnormalities in the muscle tissue, but pain processing mechanisms in the central nervous system are dysfunctional.[9] A recent review described amplification of afferent pain signals within the spinal cord as a key mechanism underlying the development of chronic pain in rheumatic diseases including (but not restricted to) fibromyalgia.[10] Psychological and social factors can contribute to this central amplification mechanism, and population studies have shown an association of such factors with the initiation and persistence of fibromyalgia.[11] However, equivalent levels of psychosocial stress are not associated with the development of fibromyalgia in all people and a genetic component is probably involved. A genome-wide linkage study of people from 116 American families with multiple cases of fibromyalgia reported that siblings of patients with fibromyalgia have a 13.6-fold (95% confidence interval 10.0 to 18.5) increased risk of developing the condition compared with the general population.[12] A single region on chromosome 17 was significantly linked to fibromyalgia in this population (P<0.001).[12]

Functional magnetic resonance imaging studies of patients with fibromyalgia have shown abnormal signalling in areas of the brain involved in processing pain and emotions, such as the amygdala, thalamus, and insula.[9 10] More recently, magnetic resonance spectroscopy was used to show increased glutamate and glutamine in the right amygdala in 30 patients with fibromyalgia compared with healthy controls, but no correlation was found between these increases and clinical features of fibromyalgia.[16]

Although these changes in cerebrospinal fluid biochemistry and cerebral signalling are associated with fibromyalgia, it is unclear whether the association is causative.

Why and how should fibromyalgia be diagnosed?

Some specialists have argued that a diagnosis of fibromyalgia is unhelpful because it overmedicalises this complex of distressing, medically unexplained symptoms.[1] But in our experience, many patients find the diagnosis helpful, especially when combined with a common sense explanation of the link between poor sleep, tiredness, and pain. Such a diagnosis can reassure patients that they do not have another, more severe illness, such as inflammatory arthritis or cancer, thereby halting a cycle of repeated normal investigations in search of a diagnosis. This allows patients to move forward and find ways of reducing the symptoms' impact on their lives.

No blood tests or imaging modalities are useful for diagnosing fibromyalgia. C reactive protein concentrations and the erythrocyte sedimentation rate are not usually raised (unlike in inflammatory arthritis), and joint radiographs are usually normal (unlike in osteoarthritis). The diagnosis of fibromyalgia is made purely on a clinical basis. Some clinicians test tenderness at the 18 sites specified in the ACR 1990 criteria. This is quick and easy to do and provides the patient with objective evidence that the diagnosis is valid. However, 25% of patients diagnosed as having fibromyalgia do not have 11 tender points.[19] The 31 point questionnaire developed from the ACR 2010 criteria is not used routinely,[6 7] although it is useful to ask patients whether they have unrefreshing sleep, tiredness, or reduced ability to think and remember clearly (sometimes called "fibro-fog"). In patients with chronic widespread pain, these symptoms strongly suggest fibromyalgia.

Fibromyalgia is not a diagnosis of exclusion and can occur together with other diseases. A population based study using the 31 point self report questionnaire found that 17% of 845 patients with osteoarthritis, 21% of 5210 with rheumatoid arthritis, and 37% of 439 with systemic lupus erythematosus fulfil the ACR 2010 criteria for fibromyalgia.[6] It is therefore advisable to examine patients for signs of these conditions before ascribing all their symptoms to fibromyalgia and to carry out a simple screen including full blood count, basic biochemistry, and inflammatory markers. Thyroid function tests and vitamin D levels may be helpful in some cases, but request autoantibodies only if the history and examination suggest that specific autoimmune rheumatic diseases—such as rheumatoid arthritis, systemic lupus erythematosus, or systemic sclerosis—should be excluded. This is because tests such as antinuclear antibody and rheumatoid factor are often positive in healthy people. For example, 13.3% of healthy adults are positive for antinuclear antibody at a titre of 1:80.[20] Positive autoantibody tests in patients with fibromyalgia but no features of autoimmune disease may be misleading. Assessment of clinical features such as tender joints in inflammatory arthritis may be complicated by coexisting fibromyalgia.[10] The diagnosis

of fibromyalgia in the presence of an inflammatory arthritis usually requires specialist advice. It is important to remember that fibromyalgia can develop in a patient who already has another diagnosis (such as rheumatoid arthritis), and this may be a reason for apparently inadequate reduction of pain in response to treatment of the pre-existing disorder.

In summary, consider fibromyalgia in a patient who has chronic widespread pain that is not fully explained by any other illness (such as cancer or inflammatory arthritis), especially if the pain is out of proportion to physical signs on examination or is associated with sleep disturbance, fatigue, or muscular tender points. Referral to a specialist is not necessary for the diagnosis of fibromyalgia,[21] but it should be considered if the diagnosis is uncertain—for example, if there is also joint swelling, rash, or Raynaud's phenomenon, which may suggest autoimmune diseases.

Treatment of fibromyalgia

Several outcome domains are of interest to patients—for example, pain, fatigue, and overall quality of life. All reported outcomes should be considered when interpreting the effects reported in systematic reviews of randomised controlled trials (RCTs). Tables 1-4 (see bmj.com) summarise the available data. For continuous outcome measures, to allow comparison across domains and between outcome measures standardised mean differences (SMD=between group difference/standard deviation at baseline) are reported. SMDs of 0.2, 0.5, and 0.8 indicate small, medium, and large effect sizes, respectively.[22]

What is the role of non-drug treatments?

Non-drug treatments can be physical or psychological (including education). Physical therapies include active (exercise) and passive approaches (joint manipulation and massage).

Physical therapies (active)

Exercise is commonly recommended in fibromyalgia,[35] and there is strong and moderate evidence to recommend specific types. A Cochrane systematic review of 34 studies that assessed the effects of exercise in fibromyalgia found that regular aerobic exercise (at least 20 min/day, 2-3 times a week for at least 2.5 weeks) improves wellbeing, aerobic capacity, tenderness, and pain compared with no aerobic exercise.[24] Strength training can also reduce pain and tenderness and improve wellbeing, although the quality of evidence is lower than for aerobic exercise (table 1).

Physical therapies (passive)

A systematic review and two clinical management papers provide moderate evidence for the effectiveness of balneotherapy (heated pool or spa treatments, with or without exercise).[24 35-37] Other passive therapies include manipulation, massage, electrotherapy and the use of ultrasound. These are often delivered by physiotherapists, osteopaths, or chiropractors. There is only weak evidence to support their use, partly because the data tend to come from small or pilot trials (table 1).[23 24 35]

Acupuncture

A Cochrane systematic review of nine trials provides evidence of low to moderate effectiveness of acupuncture.[25] It found that electro-acupuncture and manual acupuncture were no better than sham acupuncture for any outcome except stiffness at one month (six studies assessed as moderate quality, n=286). One study of moderate quality (n=58) that compared standard treatment with adjunctive acupuncture therapy found that acupuncture reduced pain in the short term (absolute reduction of 30%, range 21-39%). Four studies found no evidence for long term effectiveness for acupuncture versus control treatment after six months.[25] Acupuncture seemed safe and few adverse events were reported, but the risks are uncertain owing to the small number of participants in the trials.

Psychological therapies

In addition to exercise, guidelines for fibromyalgia recommend education and psychological and behavioural therapy. Education usually explains the nature of the condition and the underlying theory about the pain mechanisms involved in fibromyalgia. Education can provide the basis for psychological therapies, which are typically behaviourally based, such as cognitive behavioural therapy (CBT). CBT for pain management deals with the link between pain, thoughts (mood), and behaviour (negative coping strategies).[38]

There is strong and consistent evidence of the effectiveness of education for patients and carers (which usually includes advice on exercise), and most treatment programmes include some sort of education about fibromyalgia. Most studies cited used groups to deliver the education, and this may be an important element in the educational impact.[36 39]

Living and coping with fibromyalgia over a long period can have detrimental psychological effects. Mood can modulate pain perception.[38] One systematic review looked at 23 studies that included CBT as a treatment for fibromyalgia. Although the quality of evidence was low, it found that CBT was superior to control, with small benefits in reduction of pain (SMD 0.29, 0.17 to 0.49), negative mood (SMD 0.33, 0.17 to 0.49), and disability (SMD 0.30, 0.08 to 0.51) at the end of treatment. Improvements were maintained in the longer term (table 1).

Pain management and self management courses generally contain elements of education about fibromyalgia, exercise, and CBT, which are the three main non-drug treatments that are consistently effective for fibromyalgia.[40] A systematic review also provides strong evidence that combining these components and delivering multicomponent interventions (for example, those that include at least an exercise, education, and psychological component) has beneficial short term effects on key fibromyalgia symptoms.[27] CBT can be used to challenge negative or unhelpful thinking, thus enhancing the effects of other interventions—for example, by countering fear that exercise will worsen pain.

There is also moderate evidence from a systematic review and a summation of reviews of the benefit of mind-body therapies, including hypnotherapy, biofeedback, and stress reduction.[35]

How effective are drugs in the treatment of fibromyalgia?

Drugs for fibromyalgia include analgesics, opioids, and antidepressants. Some drugs, such as pregabalin, gabapentin, and serotonin and adrenaline reuptake inhibitors

TIPS FOR NON-SPECIALISTS

Fibromyalgia often occurs in patients with an existing condition such as inflammatory arthritis or osteoarthritis. In such patients, if the degree of pain is not explained by the known diagnosis, consider whether there may also be an element of fibromyalgia

It is important to explain that the aim of treatment is not to cure fibromyalgia but to reduce symptoms and improve quality of life. Some pain is likely to persist despite treatment

In patients with fibromyalgia, individual drugs are often ineffective or cause side effects so it is important to consider a change in drug or a switch to non-drug approaches, such as cognitive behavioural therapy or exercise

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

Arthritis Research UK (www.arthritisresearchuk.org/arthritis-information/conditions/fibromyalgia.aspx)—Useful leaflet on fibromyalgia; can be helpful to show this to patients during the consultation

Canadian national guidelines (http://fmguidelines.ca)—Canadian guidelines for the diagnosis and management of fibromyalgia

German guidelines (www.awmf.org/leitlinien/detail/ll/041-004.html)—German guidelines for fibromyalgia (including English version)

Resources for patients

Arthritis Research UK (www.arthritisresearchuk.org/arthritis-information/conditions/fibromyalgia.aspx)—Useful leaflet on fibromyalgia available in paper form or on the web

(for example, milnacipran and duloxetine), alter levels or the function of neurotransmitters. Different drugs may be more or less effective for different manifestations of the disorder. The choice of drug should be discussed with the patient and should target the most troublesome symptoms while taking into account any possible adverse events.[41] Multiple drugs are sometimes needed.[41]

Drugs for fibromyalgia may have apparent benefits and harms that are independent of their pharmacological action. One systematic review that pooled data from the control arms of RCTs conducted for licensing purposes found that 19% (17.4% to 19.9%) of patients had at least a 50% reduction in pain but that 11% (9.9% to 11.9%) stopped treatment owing to adverse events.[42] Similar findings are seen in the control arms of drug trials in other diseases.

Analgesics

Direct data to support the use of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) in fibromyalgia are limited.[37] In a population survey of 1799 patients with rheumatic diseases, including fibromyalgia, 60% reported preferring NSAIDs to paracetamol and 14% preferred paracetamol to NSAIDs.[43] Any decision to advise NSAIDs or paracetamol needs to take account of patient preference, comorbidities, and adverse effects.[37 41]

Opioids

The only opioid with evidence for effectiveness in fibromyalgia is tramadol (and tramadol combined with paracetamol). For tramadol on its own, the evidence is restricted to one crossover trial (n=12), which compared a single dose of intravenous tramadol with placebo over a two hour follow-up period.[44] There is only one RCT (n=315) of tramadol combined with paracetamol and this found a benefit on pain at three months (table 2).[45] Tramadol may have an additional analgesic effect through enhancing serotonin release and inhibiting adrenaline reuptake.[28 30] Although widely prescribed in primary care, there is no evidence to support the use of preparations containing weak opioids, such as codeine or dihydrocodeine, for fibromyalgia. Use of potent opioids should be avoided because of the risk of producing iatrogenic addiction.[41] Opioids do not have a specific UK product licence for use in fibromyalgia but are licensed for the treatment of pain, including the pain of fibromyalgia. The *BNF* classifies tramadol as a strong opioid, whereas Canadian fibromyalgia guidelines draw a distinction between tramadol and potent opioids.[41]

Antidepressant drugs

Many systematic reviews of RCTs show that antidepressants are effective in the treatment of fibromyalgia.[32 41] One review found pooled SMDs, compared with placebo, of 0.43 (0.30 to 0.55) for pain, 0.13 (0.01 to 0.26) for fatigue, 0.32 (0.18 to 0.46) for sleep, 0.26 (0.12 to 0.39) for depressed mood, and 0.31 (0.20 to 0.42) for quality of life (table 3, see bmj.com).[32] However, in the UK, none of these drugs is licensed for use in fibromyalgia.

A network meta-analysis of RCTs found that tricyclic antidepressants reduced pain (SMD 0.42, 0.18 to 0.65) but did not significantly affect quality of life (SMD 0.34, −0.07 to 0.74).[24] Another network meta-analysis found that the relative risk for a 30% reduction in pain from tricyclic antidepressants was 1.18 (95% credible interval 0.41 to 2.98).[28] For amitriptyline alone one meta-analysis found a 2.9 (95% confidence interval 1.7 to 4.9) relative risk for an unspecified pain reduction.[29] A network meta-analysis of RCTs found that, compared with placebo, selective serotonin reuptake inhibitors had an SMD of 0.63 (0.35 to 0.89) for pain and 0.49 (0.08 to 0.90) for quality of life.[24] Another network meta-analysis found that the relative risk for a 30% improvement in pain was 1.84 (95% credible interval 1.15 to 3.15) for fluoxetine and 1.64 (95% credible interval 1.32 to 2.04[28]) for duloxetine. A systematic review found that the SMD for duloxetine was 0.32 (95% confidence interval 0.22 to 0.41) for pain, 0.12 (0.02 to 0.23) for fatigue, 0.24 (0.12 to 0.37) for sleep problems, and 0.26 (0.16 to 0.37) for depression (table 3, see bmj.com).[30] The same systematic review found that the SMD for milnacipran was 0.20 (0.13 to 0.26) for pain, 0.14 (0.08 to 0.21) for fatigue, −0.02 (−0.10 to 0.05) for sleep problems, and 0.11 (0.04 to 0.17) for depression (table 3, see bmj.com).[30] Use of amitriptyline, fluoxetine, paroxetine, duloxetine, milnacipran, and moclobemide (a monamine oxidase inhibitor) is supported by guideline recommendations.[37 41] Moclobemide should probably be avoided owing to a high incidence of adverse events. Milnacipran is not marketed in the UK. Duloxetine is not licensed for use in fibromyalgia in the UK. Both duloxetine and milnacipran have US Food and Drug Administration approval for use in fibromyalgia, whereas in Canada only duloxetine is approved.[41]

Anticonvulsant drugs

Several systematic reviews of multiple RCTs show that the second generation anticonvulsant pregabalin is effective in the treatment of fibromyalgia.[31 34] A review of trials of pregabalin (150-600 mg/day) versus placebo found an SMD for pain of 0.28 (0.20 to 0.35), for fatigue 0.17 (0.09 to 0.25), and for sleep problems and anxiety 0.35 (0.27 to 0.43).[31] The risk ratio for a 50% pain reduction was 1.59 (1.33

QUESTIONS FOR FUTURE RESEARCH

Why is fibromyalgia diagnosed so much more often in women than in men?

Is the combination of drugs with cognitive behavioural therapy or exercise (or both) more effective than treatment with either modality alone?

Which abnormalities of central pain processing are most important in patients with fibromyalgia and can understanding this lead to better treatment strategies?

to 1.90).[31] A network meta-analysis found that when compared with placebo, pregabalin 300 mg had a relative risk for 30% improvement in pain of 1.36 (95% credible interval 1.14 to 1.64).[28] A third review found the number needed to treat with pregabalin 300 mg for a 30% reduction in pain intensity was 9.2 (95% confidence interval 6.3 to 17) and for a very good or excellent change the number needed to treat was 11 (7.3 to 26).[34]

A systematic review found one trial comparing gabapentin to placebo (n=150); compared with placebo the relative risk for a 30% improvement from gabapentin was 1.60 (1.01 to 2.53).[31]

Neither pregabalin nor gabapentin has a licence for use in fibromyalgia in the UK. Pregabalin is approved for treating fibromyalgia in the US and Canada. Guideline recommendations support the use of pregabalin or gabapentin.[37 41]

Other drugs

Many other drugs have been suggested for use in fibromyalgia. However, these drugs are used in specialist settings only and reviewing them is beyond the scope of this article

How strong is the evidence from clinical trials in fibromyalgia?

Most trials include a large proportion of women and white patients.[24] In addition, many trials have extensive exclusion factors, including psychiatric illness and chronic physical illness.[24] Thus, many patients with fibromyalgia seen in routine clinical practice may not be represented in the trial data. Because follow-up is typically short, it is not possible to comment on the risks and benefits of drug treatment beyond six months. Substantially more participants contribute to meta-analyses of different drugs than to meta-analyses of non-drug interventions. Typically, the published effect sizes of drug treatments on pain and quality of life for people living with fibromyalgia are small to moderate.[24]

The authors of a network meta-analysis concluded that the benefits of drug treatments were of questionable clinical value and that there was only limited evidence for non-drug treatments.[24] Once trials with fewer than 50 subjects per arm are excluded there is only evidence of effectiveness for one serotonin noradrenaline reuptake inhibitor (duloxetine) and pregabalin (for both pain and quality of life). Figures 2 and 3 (see bmj.com) summarise the results of this network analysis.

It may be misleading to describe effect sizes as small, moderate, large, however, because this may not relate to the individual patient. Expressing effectiveness as number needed to treat to obtain a specified outcome may be more useful clinically.[46] Clinicians and patients also need to recognise that in many cases treatment will be ineffective. If no worthwhile effect is seen after an adequate trial of a drug, it should be stopped and an alternative drug tried.[47] In the absence of any evidence for what may be an adequate trial we suggest four weeks at the full recommended dose (or the highest dose the patient can tolerate). The dose will need to be titrated upwards from a low starting point in many patients.

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References and competing interests are in the version on bmj.com.

ANSWERS TO ENDGAMES, p 36 For long answers go to the Education channel on bmj.com

ANATOMY QUIZ

Axial computed tomogram of the male pelvis

A: Right pectineus muscle

B: Bladder

C: Prostate

D. Right ischioanal fossa

E: Rectum

F: Left obturator internus muscle

Placebo controlled trials

Statement *b* is true, whereas *a*, *c*, and *d* are false.

PICTURE QUIZ Blurred vision and epistaxis

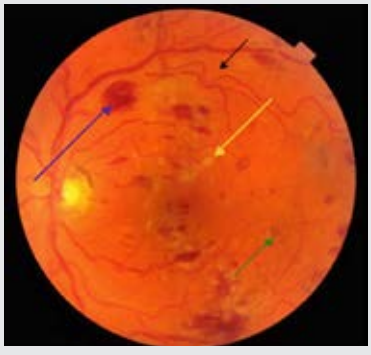
1 In light of the grossly increased white cell count, thrombocytopenia, and splenomegaly, the most likely diagnosis is chronic myelogenous leukaemia (CML). The longstanding nature of the symptoms (>3 months) is more suggestive of chronic phase CML than of blast crisis CML.

2 Diagnosis is initially based on a blood film and bone marrow aspirate or biopsy sample. The diagnosis is confirmed by cytogenetic identification of the Philadelphia chromosome translocation by routine cytogenetics/FISH (fluorescence in situ hybridisation) or detection of the BCR-ABL fusion gene using polymerase chain reaction.

3 The fundal photograph shows retinopathy of the left eye. Retinopathy is characterised by retinal haemorrhages, some of which have white centres (Roth spots), cotton wool spots, and venous tortuosity (fig 2).

4 Hypertension (especially chronic), diabetic retinopathy, or retinal vein occlusion.

5 The management of CML has been revolutionised recently by the tyrosine kinase inhibitors (TKI) such as imatinib, dasatinib, and nilotinib, which are administered orally and are associated with overall survival rates of more than 90%. Hydroxycarbamide is sometimes also used in the initial period after diagnosis if a more rapid reduction in white cell count is required.



Fundal photograph showing flame shaped intraretinal haemorrhage (blue arrow) in nerve fibre layer; blood vessels throughout retina, which appear more tortuous than normal (black arrow); focal infarcts in nerve fibre layer (yellow arrow), described as cotton wool spots; and Roth spots (green arrow), representing areas of haemorrhage around pale white centres