

Antidepressant therapy in the chronic fatigue syndrome

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SUMMARY. *The chronic fatigue syndrome is a condition receiving increasing recognition. Symptoms of depression are not infrequent and may be persistent and severe enough to warrant treatment. The controversy over the use of antidepressant therapy in this condition may present a dilemma for the general practitioner considering possible treatments. This paper draws on the literature and on the authors' own observations of patients with the chronic fatigue syndrome to suggest guidelines for the use of antidepressant therapy.*

Introduction

THERE has been much recent interest in syndromes comprising chronic, unexplained fatigue that may be long-lasting but have no recognized treatment.^{1,2} The nomenclature applied to these are varied but the term chronic fatigue syndrome^{3,4} is now widely adopted and will be used here.

The chronic fatigue syndrome^{3,4} refers to conditions of chronic disabling muscular fatigue of unknown aetiology with associated neuropsychological and physical symptoms. It encompasses conditions such as postviral (fatigue) syndrome,⁵ effort syndrome⁶ and myalgic encephalomyelitis or 'ME'.⁷ The ME Association have claimed that there may be at least 100 000 sufferers in the United Kingdom.⁸ However, precise figures of expected prevalence in general practice are not yet available.

Symptoms of depression have been reported in up to 80% of chronic fatigue sufferers.⁹ Studies looking at samples of patients with chronic unexplained fatigue using standardized diagnostic interviews indicate that at least 50% of patients in these samples would concurrently meet *DSM-III* criteria for a major depression.¹⁰⁻¹⁴ To meet such criteria it is likely that depressive symptoms are severe enough for the doctor to at least consider antidepressant treatment. Several studies indicate that the severity of depressive symptoms in such patients is similar to the level of depression that can be seen and managed in general practice.^{11,14}

The aetiology of the syndrome and its concurrent depressive symptoms is controversial.^{15,16} Some authors favour an organic cause (possibly chronic viral infection) with symptoms of depression seen as a reaction to a disabling physical disease.¹⁵ Others see this as an atypical depressive syndrome, with fatigue being secondary to these symptoms.¹⁶ Wessely has urged caution over this dichotomy, pointing out that the chronic fatigue syndrome may prove to be an even more heterogeneous condition.¹⁷

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What is agreed is that the depressive symptoms may be persistent and disabling enough in their own right to warrant treatment.¹⁸ It is surprising, however, that there are no placebo-controlled reports of the efficacy or lack of efficacy of the use of antidepressants in the chronic fatigue syndrome, or guidelines for their usage in this condition. It has been reported that these drugs are generally poorly tolerated in the chronic fatigue syndrome, owing to their sedative and autonomic side effects,¹⁹ but there are no systematic observations to refute or support this observation. However, there are reports from controlled treatment studies that antidepressant therapy may be useful in conditions thought to be related to the chronic fatigue syndrome, such as fibrositis or fibromyalgia.²⁰⁻²⁴ There is also evidence that antidepressants may have a role in the treatment of altered sleep patterns in the chronic fatigue syndrome and that low doses of tricyclic antidepressants may exert their therapeutic effect via this mechanism.²⁵

It must be emphasized that there are many possible lines of treatment for depressive symptoms and although this article will concentrate on antidepressant therapy, alternative methods may need to be considered such as psychological therapies. These have been discussed recently in this *Journal*, however, and will not be discussed further here.^{26,27}

Who meets the definition of chronic fatigue syndrome?

Fatigue is a common complaint in primary care,^{28,29} so a high index of suspicion is needed to make the diagnosis of the chronic fatigue syndrome. In general, patients with chronic disabling and unexplained muscle fatigue for at least six months may meet the operational criteria for the chronic fatigue syndrome^{3-5,30} and these patients should be carefully assessed. Various symptoms and signs may occur (Figure 1) and a comprehensive physical assessment should have been performed before diagnosis. There are many medical and psychiatric conditions which present with fatigue and which must be considered in the differential diagnosis.

The original criteria for the chronic fatigue syndrome would exclude patients with any concurrent psychiatric symptoms at the time of assessment,³ but as few patients would then meet this definition, it has been suggested that these criteria are widened to include psychiatric morbidity at the time of assessment, provided this was not thought to be the cause of the fatigue.^{30,31}

Why should antidepressants be used?

Symptoms of depression are not infrequent in the chronic fatigue syndrome¹⁰⁻¹⁴ and may compound the disability produced by fatigue. As depressive symptoms can be enduring in the chronic fatigue syndrome, such patients may also have an increased risk of suicide. We do not yet know the suicide rate for patients with this condition or the main risk factors to identify, but in patients with clear and persistent depressive symptoms we would suspect the risk will be at least as high as in depressive illness of a similar severity.

The cause of the depressive symptoms may not be understood but there is a precedent that antidepressants may be useful in treating depressive symptoms in other conditions with known organic aetiology and where there may be primary or secondary central nervous system involvement, for example in parkinson's

disease, hypothyroidism or intracerebral tumours with psychiatric manifestations.^{32,33} Such a symptomatic approach to treatment may also prove helpful in treating depressive symptoms in the chronic fatigue syndrome.

When should antidepressants be used?

There has been controversy about the assessment of depressive symptoms in the chronic fatigue syndrome.^{34,35} For example, are so-called 'biological features' of depression signs of underlying physical pathology and not truly 'depressive' in nature? Conversely, it is argued that since it is impossible to differentiate such symptoms, assessment of psychiatric symptoms in the chronic fatigue syndrome should be performed in the same standardized manner as for known psychiatric conditions.

Persistent, disabling depressed mood lasting over two weeks (and definitely over four weeks) should lead to consideration of antidepressant treatment, because by this time some patients would meet commonly used diagnostic criteria for depressive illness. Other mood states commonly associated are anxiety and irritability.¹² A list of essential symptoms to ask about are shown in Figure 2.

As fatigue is poorly understood, it cannot be assumed this is primarily a physical or psychological complaint. For this reason, it is recommended that fatigue is not included in the assessment of the severity of depression.

The psychic symptoms of depression such as lack of enjoyment or interest, pessimism and guilt, are quite specific depressive symptoms and are useful in assessment of depression in physical ill populations.³⁴

Difficulties for the patient

Attribution of symptoms

It has been reported that patients with the chronic fatigue syndrome may be more likely than depressed patients to attribute their symptoms to a physical cause.¹³ It may follow that they would find it difficult to accept that depression and anxiety may be amenable to treatment with antidepressants. This may also be due to fear of being labelled as 'not genuinely ill' and the stigma still commonly felt about receiving treatment for psychological symptoms.

An approach that we and others advocate is that the patient is left in no doubt that the validity of suffering is accepted unreservedly by the doctor.²⁶ It is then important to emphasize that when starting treatment to reduce the severity of these symptoms it is not always necessary to be aware of their cause. To elucidate this point to the patient, the following paradigms in psychiatry could be used where antidepressant therapy is used symptomatically. It could be explained that there is a physical disorder with concurrent depressive symptoms of organic aetiology. Even if the aetiology is known and the underlying condition is treated appropriately, it may not automatically follow that depressive symptoms will remit, and antidepressant therapy may still be necessary. An example of this is the treatment of hypothyroidism.³¹

Alternatively, it could be explained that there is a chronic disabling physical illness and a reactive depressive illness co-existing, which appear to be one syndrome, but in reality have different aetiologies. As before, antidepressant therapy may prove necessary if the treatment of the physical illness responds but depressive symptoms fail to do so. For example, the depressive symptoms found in multiple sclerosis and parkinson's disease may sometimes be 'reactive' rather than an integral part of the illness.³³

Definition of chronic fatigue syndrome (from Dawson 1990³⁹)

- Syndrome with fatigue as principal symptom.
- Definite onset (not life long)
- Fatigue is severely disabling and affects physical and mental functioning
- Other symptoms may be present, particularly myalgia, mood disturbances, sleep disturbance
- Minimum six months of fatigue present at least 50% of time

Suggested baseline investigations

After comprehensive physical examination, including central and peripheral nervous system:

- Haematology: haemoglobin and other parameters, differential B12 and folate, monospot
- Biochemistry: profile of serum urea and electrolytes, glucose, liver and thyroid function, muscle (including cardiac) enzymes
- Virology/bacteriology: at present this is controversial, but the most widely reported screening tests are for monospot and the VP-1 antigen if available.

Psychiatric assessment

Psychiatric diagnoses ought to be considered:

- If depressive or anxiety symptoms are prominent and could predate the onset of symptoms
- If there is a strong family psychiatric history or past psychiatric history OR
- If the somatic complaints are bizarre or inconsistent.

Figure 1. Definition and investigation of chronic fatigue syndrome.

Antidepressant therapy can be considered if three or more of the following symptoms and complaints (excluding fatigue) have been present most of the time for over two weeks.

Biological symptoms

These should represent a recent change in the clinical picture of the fatigue syndrome.

- Appetite decrease (or increase) with weight loss (or gain)
- Sleep disturbance (usually decrease in number of hours sleeping but can be increase)
- Decrease in libido

Psychic symptoms

- Pessimism
- Guilt (unrealistic in nature)
- Worthlessness
- Lack of enjoyment
- Recurrent suicidal ideation or ideas of death
- Concentration difficulties (of recent onset)

The presence of severe, generalized anxiety symptoms may lead to difficulty. If these are prominent but depressive symptoms are mild, then antidepressants may still be useful. Disturbance of concentration has been considered part of the chronic fatigue syndrome, but if this is of recent onset and there are no features suggesting a relapse of symptoms it may be considered as a depressive symptom.

Figure 2. Assessment of depressive symptoms in chronic fatigue syndrome.

Fears about the antidepressant drug

Fears about treatment are commonly of several kinds: that the antidepressant will make symptoms worse, that it will not work, that if it does work it will not be possible to stop the drug without a relapse.

There are anecdotal reports that in some cases of the chronic fatigue syndrome, patients may tolerate first generation tricyclic

antidepressants poorly owing to the sedation and they may experience exacerbation of fatigue symptoms.¹⁹ Postural hypotension may also be more of a problem, especially as many patients will already have had prolonged bed rest which in itself increases the risk of postural hypotension. It is our experience that these problems are reduced using lower initial dosage and slower rates of increase in dosage and that antidepressants can be tolerated. Certainly, from a survey of 75 patients who had previously taken, or were taking antidepressants, it appeared that tricyclic antidepressants with more potent autonomic side effects, for example imipramine, are more associated with problems.³⁶ However, newer tricyclic agents such as lofepramine,³⁷ 5-hydroxytryptamine uptake inhibitors, for example fluoxetine,³⁸ and newer monoamine oxidase (MAO) inhibitors such as moclobemide³⁹ may prove to have advantages as they are generally not sedative and have few autonomic side effects.

Our observations from systematic follow up of 50 patients with the chronic fatigue syndrome treated with lofepramine hydrochloride and fluoxetine, on the basis of the severity of their coexistent depressive symptoms, indicates that these agents have some effect in treating depressive symptoms of mild to moderate severity.³⁸ Over a third of such patients (on either drug) showed a 50% or greater reduction in the severity of depressive symptoms by eight weeks of treatment and another third a 50–25% reduction in symptom severity.

Of 25 out of 30 patients (17 on lofepramine, 13 on fluoxetine) who responded to antidepressant therapy, treatment could be stopped without relapse of depressive symptoms up to six months after discontinuation. This would indicate that it is possible to discontinue such drugs in the same manner as has been recommended for patients with depressive illness.

Expectation of total 'cure'

There are anecdotal reports of 'cure' of all symptoms of the chronic fatigue syndrome using antidepressant therapy. Our view is that there is no evidence to substantiate these claims. From our observations, symptoms of fatigue and myalgia may improve concurrently with symptoms of depression and anxiety in some cases of the chronic fatigue syndrome. However, such improvement is not universal. Patients taking antidepressant therapy could be advised that there is a good chance of improvement of depressive symptoms, but that the benefit for fatigue and myalgic symptoms is not presently clear. This may also help clear the misconception held by some patients that if they improve this means all the symptoms were 'in their mind'. It is equally possible that depressive symptoms will have heightened the chronic fatigue syndrome patients' perception of their fatigue and myalgic symptoms. If so, some degree of improvement would be expected in these complaints when the coexistent depression remits.

Difficulties for the physician

Choosing an antidepressant

Antidepressants can be categorized as regards their potential use in treatment of depression in chronic fatigue syndrome patients (Table 1).

The choice of drug depends not just on the profile of depressive and anxiety symptoms, but on the profile of fatigue symptoms which may be affected. Fluoxetine and lofepramine have fewer sedative or autonomic nervous system effects.

Expected side effects and adverse effects

From our experience and that reported in the literature, signifi-

Table 1. Types of antidepressant and their indications for use in the chronic fatigue syndrome. This list is not exhaustive and contains drugs now commonly prescribed in general practice or likely to be commonly prescribed in the near future.

Property and type of antidepressant	Example	Indication
<i>Sedative</i>		
Tricyclic	Amitriptyline ^a Dothiepin ^a	When fatigue mild but anxiety severe
Tetracyclic	Mianserin	
<i>Neutral (not sedative)</i>		
Tricyclic	Imipramine ^a Lofepramine	When fatigue more severe and anxiety less severe
5HT uptake inhibitor	Fluoxetine Fluvoxamine Paroxetine	
MAO inhibitor	Phenelzine ^a Meclobemide	

^aThese drugs have significant autonomic side effects. NB: Caution is required when changing between MAO inhibitor and tricyclic and/or 5HT uptake inhibitor. See *British national formulary* recommendations. L-tryptophan has been omitted as there is still controversy over its implication in producing myalgic side effects and this issue had not been satisfactorily clarified at the time this paper was written. Lithium therapy may be considered where there is recurrent depression, but is not mentioned as a first-line antidepressant as there is little work on this role in chronic fatigue syndrome.

cant and distressing side effects from antidepressant therapy will occur in under 10% of patients with the chronic fatigue syndrome; a figure which is not greatly different from that found in studies of patients with major depression.^{37,38}

Sedative effects are generally noticed earlier on if these are to become prominent. With tricyclic drugs such as lofepramine there may be a dose-related effect more noticeable on the final higher dose. With fluoxetine, sedation is sometimes a problem of later stage treatment. If this is an early and persistent side effect it is worthwhile changing antidepressant as these side effects may not diminish and in any case compliance by the patient will be poor. If this is a late effect then it is worthwhile decreasing the dosage of drug (for fluoxetine this would mean an alternate day as opposed to once daily regimen).

The other main problem is autonomic nervous system effects. Postural hypotension seems to be over-represented in patients taking the older generation of tricyclic drugs (in 5–10% of patients we have seen on such drugs), even at lower doses. Anticholinergic effects are more noticeable in the first week and are more common with higher doses of tricyclics or monoamine oxidase inhibitors. The commonest reported autonomic side effects are blurred vision and dry mouth.

Other side effects include nausea, which may occur with any drug, but at low dosage is more common early in treatment with highly selective 5HT uptake inhibitors such as fluvoxamine. Agitation and tremor are usually only rarely reported and occur more commonly with higher dosage (particularly for 5HT uptake inhibitors).

Suggested regimens for antidepressant therapy

There is no available evidence to date of a higher than normal risk of adverse drug reactions in this group of patients, but consideration ought to be given to repeating haematological and biochemical tests if adverse reactions are suspected. These results

can be compared with baseline investigations which should in any case already have been performed to conform with this diagnosis.

As others have suggested²⁶ a simple symptom checklist to detect possible side effects or adverse effects is useful, as these effects may be difficult to differentiate from some pre-existing somatic symptoms. Antidepressants should be started in low doses for the first two weeks (for fluoxetine and drugs with long half-lives this means a twice weekly or alternate-day regimen). Further dosage increases up to recommended limits can be performed fortnightly.

With this sort of stepwise regimen, response to treatment is likely to occur by about six weeks. Some noticeable improvement may occur by two weeks. Among the first symptoms to improve are somatic anxiety symptoms and disturbance of sleep and appetite. If after an eight to 12 week period at *British national formulary* recommended doses there is no discernible response, it is recommended that the type of antidepressant is changed. With adequate patient compliance, failure to respond to one tricyclic agent in our experience tends to predict failure to respond to other tricyclics. A different class of antidepressant such as a monoamine oxidase inhibitor or a 5HT uptake inhibitor should be considered in this case.

Expected response rates to antidepressants cannot be firmly established until there are placebo-controlled trials, but our initial impressions are that these may approach those seen in depressed patients with a similar severity of depression. Patients with very mild symptoms generally do not respond as well.

Conclusion

There is some evidence that antidepressants can be of benefit in patients with at least moderately severe symptoms of the chronic fatigue syndrome. There is a need for further prospective studies of antidepressant therapy in this group of patients; particularly placebo-controlled studies. Further research needs to be done to determine which groups of patients will show most benefit from this treatment.

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