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REVIEW ARTICLE

Fatigue, depression and chronic hepatitis C infection

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ABSTRACT

Background. We aimed to determine if an association exists between uncomplicated hepatitis C virus (HCV) infection and depression or fatigue.

Method. A review of the literature was undertaken.

Results. There is an association between HCV infection and either depression or fatigue in certain circumstances – those who are aware they are HCV positive, those with advanced liver disease and those seen in specialist referral centres. All these studies are subject to important biases. There are only a few studies in which knowledge of HCV status and assessment of fatigue or depression is independent. These studies do not suggest an association. There is no association between conventional markers of liver disease and depression or fatigue.

Conclusions. Despite anecdotal evidence to the contrary, at the moment there is no evidence that HCV infection *per se* is associated with fatigue or depression, and there is a suggestion that it is not. The same risk factors that exist for fatigue in other physical illnesses, such as metabolic disorder, mood disorder, demographics and lack of exercise, certainly exist for HCV. Although there are elegant theoretical mechanisms, there is no compelling epidemiological evidence for an additional HCV specific fatigue or depression factor.

INTRODUCTION

In this paper we shall address the question of the relationship, if any, between hepatitis C virus (HCV) infection and on the one hand fatigue, and on the other depression. In this review we shall follow convention and define fatigue as a subjective symptom, and depression as a syndrome.

Although fatigue and depression are different symptoms and constructs, there is considerable overlap between them. To put it at its simplest, a minority, albeit a substantial minority, of those who complain of fatigue will also be depressed, but nearly everyone with depression will also experience fatigue (Wessely *et al*. 1998).

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METHOD

Several different search strategies and sources were used. On MEDLINE for depression the complete search strategy devised by the Cochrane Collaboration Review Group for Depression, Anxiety and Neurosis was used covering depression, depressive disorders, dysthymia, adjustment disorder, mood disorder and affective disorder. This was joined to a similar strategy used by the Cochrane group for chronic fatigue syndrome, involving all combinations of chronic fatigue, chronic fatigue syndrome, neurasthenia and synonyms, linked to a keyword search on fatigue. This was then run against a keyword search on hepatitis and all hepatitis virus sub-headings. Similar search strategies were used on PSYCHLIT and citation searches performed on the Science and Social Science Citation Indices at Web of Science.

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THE QUESTION

At first sight the question seems clear. Many hepatologists report that fatigue is indeed common in patients with HCV, and rarely question the validity of the association. There are frequently expressed opinions that fatigue is a particular issue in HCV infection, implying some unique fatigue inducing property of the infection. Uncontrolled studies seem to confirm this – for example 81% of women infected with HCV as a result of the anti-D immune globulin contamination episode in Ireland reported fatigue (Kenny-Walsh, 1999). In another series from America 67% of patients with post-transfusion HCV reported initial fatigue (Tong *et al*. 1995). Other series report fatigue as 'common in all stages of infection' (Lee *et al*. 1997). However, several caveats are needed before we can accept this as proven.

First, fatigue is common. There are far too many studies to cite that confirm that fatigue is one of the commonest somatic symptoms experienced in the community, let alone primary or secondary care (see Wessely, 1995; Wessely *et al*. 1998). As fatigue is normally distributed in the community (Pawlikowska *et al*. 1994) the exact prevalences depend upon sample and case definition, but a typical United Kingdom study will report that about 30% of women and 20% of men will complain of feeling tired all the time, every day for the previous month (Cox *et al*. 1987). Thus, American blood donors who had been found by chance to have HCV infection seemed to have high rates of symptoms – 61% for example complained of fatigue, 54% headaches and so on (Shakil *et al*. l995). Clinicians could be forgiven for concluding these rates must be linked to HCV infection. But the same group later looked at symptoms experienced by healthy blood donors without HCV and found, one suspects to their surprise, that the rate of fatigue in the non-HCV donors was actually higher (70%). Of all the somatic symptoms, only abdominal pain, itching and dark urine were commoner in the HCV positive donors. Fatigue and depression were not (Hoofnagle, 1997).

Even at the extremes many will be surprised by just how common chronic debilitating fatigue is in the population. A recent study found that over 40% of people who had experienced an acute infection with Q fever now fulfilled criteria for chronic fatigue syndrome (a prolonged and disabling form of fatigue (Fukuda *et al*. 1994)) – but this apparent strong association was somewhat diminished by the finding that 26% of the apparently normal controls, randomly chosen from the population, did so as well (Ayres *et al*. 1998).

Secondly, it is important to distinguish between psychological reactions to the knowledge that one has been infected with HCV, and the direct effects of the virus itself. Learning that one has contracted a serious infection such as HCV, with its implications for future health and behaviour, is a major life stressor, and will produce emotional stress in most, and psychiatric disorder in many. This is suggested by one small study, which compared 15 patients who were aware of their HCV status with 19 patients who were not aware (Rodger *et al*. 1999). Those who were unaware of their status reported higher (i.e. better) values on all of the eight scales that make up the SF-36, a commonly used generic measure of quality of life, although statistical comparisons were not made.

Thirdly, HCV is a major cause of liver disease. Liver disease, like most serious somatic illnesses, is itself associated with fatigue via a variety of mechanisms. Hence, an association may not be due to any direct effect of the virus, but as a by product of the consequences of hepatic disease. Related to this is the issue of selection bias – specialist/tertiary care naturally attracts the more severe end of the spectrum, and any study based entirely in tertiary care will inevitably report more associations between the exposure in question and the clinical outcome – sometimes called the 'Clinician's Fallacy' or 'Berkson's Bias' (Cohen & Cohen, 1984). Again, this is observed across clinical medicine and is not unique to this situation.

Finally, clinicians tend to overestimate the impact of new illnesses on quality of life, as indeed is pointed out in the hepatitis literature. Foster and colleagues (1998) compared hepatitis B infected patients with HCV infected patients. There were quite marked differences in quality of life between the former and latter. An accompanying editorial made the interesting point that the values for the hepatitis B patients were actually surprising low, in contrast to previous studies of physician-rated quality life

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of life, implying a general tendency for physicians to overestimate the effect of a new disease, or alternatively to underestimate the coping skills of their patients (Owens, 1998).

STUDY DESIGN

There are many different methodologies for addressing the question of the relationship between fatigue and/or depression and infection. This is a subject that we have addressed on many occasions when the question of such a link has been raised for other infective agents (Wessely, 1991; Wessely *et al*. 1995).

The weakest design is the simple case series, in which a series of patients known to have HCV infection is examined or questioned for the presence of fatigue or depression. This is subject to numerous biases. First, most such studies do not include representative samples of those with hepatitis – with a bias towards the more clinically severe cases, in which any association will be exaggerated. Secondly, patients are aware of the diagnosis, and thus it is impossible to separate out the psychological impact of the diagnosis from the direct effects of the infection. For example, a study reported that most psychological and symptomatic problems appeared 'once the diagnosis was made' (Taruschio *et al*. 1996), but without the appropriate design such observations cannot be confirmed. Thirdly, many have low response rates. Fourthly, case series without controls are difficult to interpret. Several studies in this field make reference to expected levels in the community, but comparisons with normative values established by different investigators in different settings, even if using similar instruments, are notoriously unreliable.

Case–control series have some advantages, particularly if the controls are chosen with a similar, but not identical, diagnosis, such as those with liver disease not due to hepatitis. However, case–control studies are also difficult to execute in a way that is free from bias. The particular modes of acquisition of HCV (for example drug abuse) may cause significant confounding (a confounder is something associated with both exposure (HCV) and outcome (for example depression)) and are thus an alternative explanation for an observed association between HCV and depression.

Two other designs are superior. One uses surveys in which patients have their exposure status (i.e. HCV status) assessed independently of knowledge of their symptoms or clinical status. Examples would be assessments of hepatitis status ascertainment in patients presenting with fatigue and/or depression. Confounding effects are still a problem in this type of study – for example, if the cause of fatigue or depression was also associated with an increased risk of hepatitis – studies of substance misuse populations would be prone to such bias. Random population samples are preferable, for example blood donors, in which symptoms and HCV status are assessed entirely independently, and in random samples of the population. Hence, the American study of blood donors already cited (Hoofnagle, 1997), which failed to show differences in fatigue and depression between HCV positive and negative blood donors must be given considerable weight.

RETROSPECTIVE STUDIES OF PATIENTS WITHOUT KNOWN HEPATITIS

Some studies using this design have produced evidence in favour of an association between hepatitis and depression and/or fatigue. Rivera and colleagues (1997) found that patients with fibromyalgia, a somewhat controversial diagnosis made by rheumatologists but certainly associated with generalized fatigue and myalgia, were more likely to be HCV positive than rheumatoid controls (15·2 *v*. 5·3%).

On the other hand, in a study of drug abusers, in which subjects were assessed for depression and HCV status simultaneously, there were no important differences in levels of depression between those found to be HCV positive and those negative. One out of four subscales (positive affect) was different, but as this was a *post hoc* subgroup analysis the results must be interpreted with great caution (Johnson *et al*. 1998).

Likewise, two studies exist of patients presenting with chronic fatigue syndrome, in which hepatitis status was assessed retrospectively, thus avoiding confounding due to the psychological impact of the diagnosis of HCV. No study reported any association (Dale *et al*. 1991; Mawle *et al*. 1995).

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We have already drawn attention to the problem of the psychological impact of knowing one's diagnosis. One study addressed this directly. Rodgers and colleagues (1999) compared not only those aware *versus* those unaware (and found that the former scored worse on every subscale of the SF-36), but also compared the unaware group with the general population. Those who were unaware of their status differed from population norms on only three out of eight subscales of the SF-36, those referring to mental health and vitality. The authors interpret this as showing that these symptoms may be secondary to a physiological, infection-related mechanism. However, as the sample was entirely drawn from injected drug users, this does not follow, since it may still be the result of confounding by source of infection.

STUDIES OF PATIENTS WITH KNOWN HEPATITIS

Sherman and colleagues (1999) found that patients with known HCV reported a worse quality of life, more depression and more fatigue than normal controls. In a study comparing HCV with hepatitis B patients, SF-36 scores, including physical symptoms and functioning, including fatigue, were worse in the HCV cohort (Foster *et al.* 1998). However, the groups also differed on other factors, such as gender, which might explain the findings. Barkhuizen and colleagues report that in hepatology outpatients, fatigue was found in 67% of HCV positive compared to 44% of HCV negative patients, a significant association (Barkhuizen *et al.* 1999). Patients with liver disease due to HCV had more symptoms, fatigue and depression than those with end stage liver disease from other causes (Singh *et al.* 1997), although quality of life scores did not differ. However, patients with end-stage liver disease awaiting transplantation are not appropriate to determine the effect of HCV infection *per se* on the risk of fatigue and/or depression.

Other studies suggest the link may be more complex. In a study of patients with haemophilia Weaver and colleagues showed no differences in mean levels of fatigue between patients free from the virus, those who were antibody positive, and those who were polymerase chain reaction (PCR) positive (Weaver *et al.* 2000). Only the criteria for chronic fatigue syndrome were more frequently fulfilled in those who were PCR positive, which may reflect the increased rate of myalgia type symptoms seen by several groups (Goulding *et al.* 1988; Barkhuizen *et al.* 1999; Cacoub *et al.* 1999). Likewise, in the well researched Irish anti-D HCV cohort, although fatigue was significantly increased in HCV patients compared to controls, there was no difference between those who were PCR positive and PCR negative (Goh *et al.* 1999). These studies raise the possibility that active viral replication *per se* is not closely associated with fatigue.

Finally, several studies have detailed the many psychological reasons why patients who are aware they have HCV may have increased rates of psychological distress, sometimes with anxiety more prominent than depression. These include fears of the future, risk of cirrhosis and/or cancer, concerns about transmitting the infection to relatives, worries about complications of treatment and so on (Taruschio *et al.* 1996; Zickmund *et al.* 1999).

ARE THERE HEALTHY CARRIERS?

Another piece of the jigsaw comes from studies of asymptomatic individuals found on routine investigations to be positive for HCV. The phenomenon of HCV-antibody positive individuals with consistently normal liver function tests is well recognized. Even though some have mild liver disease, many are free from symptoms, including fatigue. For example, an Italian group studied 23 individuals reported as being symptom free, but positive for anti-HCV (Alberti *et al.* 1992). The majority turned out to have liver involvement. Thus, although this study challenges the notion of healthy carriers (the term is probably a misnomer (Hoofnagle, 1997)), in that they actually had occult liver disease, it does not challenge the notion of asymptomatic carriers. Four healthy carriers were reported in another Italian study, although it is not specifically stated they were symptom free (Brillianti *et al.* 1993). A Spanish series identified 975 blood donors positive for anti-HCV antibody. Although clinical details are sparse, all would appear to be asymptomatic (Prieto *et al.* 1995). Sadly, the opportunity to perform what

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would be a definitive case–control study in this population was not taken.

All one can conclude from these studies is that it is possible to have HCV infection, and even occult liver disease, without fatigue or depression. Clearly, HCV, fatigue and infection are not synonymous.

ASSOCIATIONS OF FATIGUE

Whatever it is that is associated with fatigue, it is not the degree of liver involvement or damage. No correlation between fatigue and measures of liver damage was found by virtually every study that has considered the matter (Mahl *et al*. 1996; Nelles *et al*. 1996; Foster *et al*. 1998; Poynard *et al*. 1998; Barkhuizen *et al*. 1999; Goh *et al*. 1999; Lau *et al*. 1999; Kraus *et al*. 2000; Dwight *et al*. 2001), with one exception (Desmorat, 1998), and this gives us one of the few confident findings in this field. Instead, fatigue in HCV is correlated with the same factors that would be found in community non-HCV samples – for example gender, increasing age and weight loss (Poynard *et al*. 1998; Lau *et al*. 1999).

This should come as no surprise. If we consider other physical illnesses in which fatigue plays a prominent part, nearly all studies fail to show a simple relationship between measures of disease activity and degree of fatigue. Yet most studies fail to link measures of individual disease activity with subjective fatigue – instead depression, illness beliefs, lack of activity and so on figure more prominently in studies of primary biliary cirrhosis (Cauch-Dudek *et al*. 1998), SLE (McKinley *et al*. 1995; Wang *et al*. 1998), HIV (Ferrando *et al*. 1998) and rheumatic diseases (Wolfe *et al*. 1996). In our review of the subject we concluded that 'many studies suggest that direct and specific biochemical or physiological measures of disease activity are not important predictors of fatigue (Wessely *et al*. 1998). The default position is therefore to assume that HCV infection *per se* is not a significant cause of fatigue until proved otherwise, the opposite of the approach taken by some clinicians who specialized solely in liver disorders.

QUALITY OF LIFE AND DEPRESSION

Quality of life (QOL) is a relatively recent concept that has rapidly acquired both importance and an extensive literature. Foster provides a recent review pertinent to HCV (Foster, 1999) as well as a data-based study (Foster *et al*. 1998). The data-based study found a significant reduction in QOL between HCV and hepatitis B infected patients. Foster's review noted that seven studies found an association and one did not. A further study not included in the review did not find an association (Singh *et al*. 1997), and specifically did not find a difference in QOL scores between patients with HCV and those with other liver diseases (Singh *et al*. 1997), but the sample was not ideal for this purpose.

Recently, one of us has completed a study on the treatment of interferon-alpha in patients with chronic viral hepatitis B and C, with or without a psychiatric diagnosis before starting interferon-alpha therapy (Pariante *et al*. 1999). The main published finding has shown – using survival analysis – that patients with a current or a previous psychiatric diagnosis before starting interferon-alpha were not more likely than patients without a psychiatric diagnosis to interrupt the interferon-alpha therapy (Pariante *et al*. 1999). For the present review, we have analysed the baseline psychiatric diagnosis and the type of virus in 57 subjects from the study. We have found that more patients with HCV (14 out of 39, 36%) had a psychiatric diagnosis at baseline (mostly an anxiety or a depressive disorder) compared to patients with hepatitis B (2 out of 18, 11%) (chi-square = 3·74, df = l, $P = 0{\cdot}048$). Patients with HCV were more likely to be females (36%) compared to B (11%). However, these higher rates of psychopathology in patients with HCV were confirmed by analysing the male sample only (28% in C *v.* 11% in B, not statistically significant) (unpublished observations).

Once again, all such studies are heavily confounded by the same biases already discussed. Nevertheless, it is reasonable to conclude that patients with known HCV infection attending specialist centres do have a reduction in their general sense of well-being, but whether or not this is because they are aware of their infection, or are a more severe subgroup, cannot be determined. Likewise, it is too early to say if this represents a distinct property of HCV infection over and above other chronic hepatic conditions.

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DEPRESSION

All the arguments outlined above about the difficulties in determining the extent and nature of the relationship between fatigue and HCV apply in equal measure to depression. For example, the well regarded Seattle group report that 28% of those with HCV fulfil criteria for major depression (Dwight *et al*. 2001), a figure in excess of expected community values. However, this kind of study has many limitations, as the authors admit. The setting is a specialist one. The response rate (47%) is disappointing, suggesting that biases have been introduced – either those who are more sick being more likely to co operate, or alternatively the reverse. Either way, the figure of 28% is likely to be inaccurate. The comparison with expected values in the community is unsatisfactory. All patients know the diagnosis, so the influence of the psychosocial disturbance from receiving the diagnosis cannot be determined.

Likewise, although in Ireland 26% of those with HCV as a result of receiving contaminated blood in Ireland reported 'clinical levels of depression', but without controls this is impossible to evaluate (Birchard, 2000). 'Over a quarter' of the cases reported by Lee and colleagues (1997) were noted to be 'depressed', but no standardized instruments or definitions were reported. This is crucial, since although community studies using the most modern instruments, interviews and definitions usually give lower prevalences, there are plenty of well-conducted community or primary care based studies, particularly if questionnaire based, that report similar prevalences to those observed in the cited HCV studies.

Attention has already been drawn to the study of Johnson and colleagues of HCV in drug abusers, which failed to find important differences in levels of depression between those found to be HCV positive and those negative (Johnson *et al*. 1998).

Depression is not the only psychiatric disorder. Two abstracts tantalizingly report higher levels of anxiety than depression in HCV patients (Taruschio *et al*. 1996; Zickmund *et al*. 1999). Without more data and studies it is impossible to interpret these preliminary observations further.

Reviews of the subject have not been able to reach any clear conclusions. One review merely stated that psychiatrists can expect to see increasing numbers of patients with HCV referred for consultation, an uncontroversial conclusion, but one that does not add to this debate (Yates & Gleason, 1998). The authors felt that more research was needed. Similarly, Foster was only able to conclude that 'further studies will be required to determine the role of depression in patients with chronic HCV' (Foster, 1999), a view we endorse.

RESPONSE TO TREATMENT

Another approach is to study the response to treatment. Does clearing the virus lead to an improvement in either fatigue or depression? Probably yes. Clearing the virus is associated with self-reported improvement in quality of life in several studies (Bonkovsky & Wooley, 1999; Ware *et al*. 1999; Neary *et al*. 1999). One study reported that 'all patients who had fatigue before treatment (60%) said that the fatigue completely disappeared after treatment' (Marcellin *et al*. 1997). That is, however, a remarkable result, since that means that the patients are now far better than a normal random population. Likewise, we also know that long-term survivors of, for example, cancers associated with fatigue, continue to show persistent high levels of fatigue long after complete resolution of the cancer (Jacobsen & Stein, 1999; Loge *et al*. 1999). Instead, this may be an example of response bias. Finally, recurrence of HCV in post-transplant patients is associated with worse quality of life and depression (De Bona *et al*. 2000; Paterson *et al*. 2000).

It seems however that when patients clear the virus they experience an improvement in quality of life, even if it is improbable many become symptom free. But the finding that symptoms improve after clearing the virus do not mean that it was the virus *per se* that was responsible for symptoms directly – it could still be the psychological effect of knowing one's future prognosis has improved. In only one study were patients blinded to the results of the PCR tests (Bonkovsky & Wooley, 1999), and even then patients were aware of their liver function tests. It is probable that most patients will be aware that a failure for liver function tests such as ALT to show improvement is very likely to be an

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indicator of failed treatment response, and vice versa.

POSSIBLE MECHANISMS

One of the reasons why investigators have been so taken with a possible link between HCV and fatigue is the variety of mechanisms that one can postulate to explain such a link, if it were to be proven. We have mentioned already that various psychological mechanisms may account for the possible increased presence of depression and fatigue in patients with chronic viral hepatitis. An alternative mechanism is that changes in the immune system – due to the viral infections and to the chronic liver diseases – may directly cause depression and fatigue, through a direct effect of cytokines on the nervous system.

As in other viral infections and chronic liver disease, some studies have described increased production of cytokines, especially of the pro-inflammatory cytokines interleukin (IL)-1, IL-6 and tumor necrosis factor in patients with viral hepatitis B and C (Tilg *et al.* 1992; Gonzales-Amaro *et al.* 1994; Fukuda *et al.* 1995; Shindo *et al.* 1996; Huang *et al.* 1999). Specifically, these studies have found increased pro-inflammatory cytokine serum levels (Tilg *et al.* 1992; Huang *et al.* 1999) and increased pro-inflammatory cytokine production by the liver (Gonzales-Amaro *et al.* 1994; Fukuda *et al.* 1995; Shindo *et al.* 1996). Pro-inflammatory cytokines, produced in the context of infections or immunological therapies, have been described to induce a non-specific behavioural syndrome referred to as 'sickness behaviour'. This syndrome comprises anhedonia, anorexia, fatigue, diminished activity, weakness, inability to concentrate, sleep disturbance and impaired cognition (Kent *et al.* 1992). Moreover, pro-inflammatory cytokines may stimulate the release of corticotropin releasing hormone (CRH) and cortisol, thus inducing a hyperactivity of the hypthalamo–pituitary–adrenal axis similar to that described in patients with major depression (Kent *et al.* 1992). Interestingly, major depression has also been associated with increased levels of pro-inflammatory cytokines (including IL-1) (Maes *et al.* 1993).

Hence, it is possible that depression and fatigue in the context of viral hepatitis are related to sickness behaviour, and to the endocrine changes elicited by the pro-inflammatory cytokines. However, some studies have reported normal serum levels of pro-inflammatory cytokines in asymptomatic chronic hepatitis B carriers (Kakumu *et al.* 1989) or during the recovery phase after acute viral hepatitis (Torre *et al.* 1994). Moreover, reduced production of pro-inflammatory cytokines by peripheral blood monocytes of patients with chronic viral hepatitis has also been described (Muller & Zielinski, 1992; Muller *et al.* 1993). Finally, one study that looked at levels of pro-inflammatory cytokines and fatigue in chronic HCV patients found increased levels of IL-1, IL-6 and TNF but no relationship with fatigue (Gershon *et al.* 1998). Therefore, the hypothesis that pro-inflammatory cytokines are related to depression and/or fatigue in these patients is tempting, but speculative.

CONCLUSION

The main conclusion of this review is that it is we cannot at present be certain of the relationship between fatigue, depression and HCV. We believe that the evidence reviewed above tends to favour the null hypothesis of no direct relationship, but this is by no means established beyond reasonable doubt.

There are a number of reasons for this. The simplest is that it takes time to unravel complex epidemiological associations. It is far simpler to answer questions such as the relationship between HCV and outcomes such as death – since measurement issues are simpler. Likewise, determining the relationship between HCV and cirrhosis is simpler, since the outcome is relatively unusual in the general population, and although there are certainly other explanations, fortunately there are not too many of them, and these too are relatively easy to measure. None of the above is true for either fatigue or depression – both present substantial issues of measurement, none of them resolved, both are remarkably common anyway, and both have numerous overlapping causes.

The large number of abstracts and preliminary communications in the reference list strikes a further note of caution. It remains to be seen whether or not the data contained in these abstracts is sustained in a full, peer reviewed publication. Likewise, although it is clear that

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important cohort studies now exist that might shed light on these relationships, to date investigators have been more concerned with 'hard' endpoints such as cirrhosis, transplanation and death, and until now have not recorded 'softer' outcomes such as those considered in this paper.

All we can say with some certainty is that many patients with advanced HCV and associated liver disease are also troubled by clinically significant depression and fatigue (Zdilar *et al*. 2000). In cases where patients have advanced liver disease, and perhaps are heading towards transplantation, numerous causes exist, such as the debilitating effects of liver failure, the side effects of treatment, and the knowledge of further complications and even mortality. In such cases assuming a causal relationship between some aspect of HCV and fatigue/depression is probably safe. However, the key word is 'some'. Deciding exactly what is the mechanism is far less simple. In patients with HCV infection, and either liver disease of lesser severity, or alternatively no apparent liver dysfunction at all, it is too early to say whether or not such an association exists.

The general literature on fatigue and physical disease should also suggest caution. Overall, examples of specific associations between a known agent and fatigue are less common than more general links. It is true that such links have been shown on occasion, and it is also true that plausible mechanisms exist to suggest such a link might be present for HCV. However, past experience and the wider fatigue literature suggests that the odds do not favour such a specific association being sustained.

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