Does prophylactic antidepressant treatment boost interferon-alpha treatment completion in HCV?

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Abstract

Depression is often a side effect of interferon-alpha treatment for hepatitis C, and is recognized as a cause for treatment discontinuation. When detected, antidepressant treatment begins promptly. In contrast to this rescue approach, prophylactic antidepressant treatment has been considered as a superior approach. While studies indicate that depression is lower with prophylaxis, no study has prospectively evaluated the degree that treatment completion might be boosted by the prophylactic strategy. A structured literature search was conducted to discover all trials of antidepressant prophylaxis for patients undergoing antiviral treatment for chronic hepatitis C. Selection criteria included: antidepressant prophylaxis study; report of depression treatment outcome; report of numbers discontinuing and reason for discontinuation (including any of the following: discontinuation data for medical side effects (i.e., thrombocytopenia); discontinuation due to lack of antiviral response; discontinuation due to lack of antidepressant effect; discontinuation due to antidepressant side effects; discontinuation due to patient preference; discontinuation due to loss to follow-up; or unspecified discontinuation). Across the studies, total enrollees were determined for the prophylaxis arms and the rescue arms, and then, again across studies, those discontinuing for reasons other than lack of antiviral response or medical side effect were summed for each of these two arms. Twelve studies were discovered. One was a retrospective chart review, one was an uncontrolled trial, and ten were controlled trials. Discontinuation of antiviral therapy was not less common in the prophylaxis arms: of the 396 patients treated by the prophylaxis strategy, 47 (11.9%) discontinued; of the 380 patients in the rescue strategy, 45 (11.8%) discontinued. While the prophylaxis strategy seems to manage depression symptoms, it does not seem to boost treatment completion. Rescue was a very successful strategy when indicated. While antidepressant prophylaxis has benefit in antiviral treatment, it should not generally be valued for boosting the likelihood of treatment completion.

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Key words: Depression; Therapy; Clinical; Psychiatry

Core tip: To inform clinical practice, this narrative review summarizes existing evidence regarding the degree that antidepressant prophylaxis boosts hepatitis C antiviral treatment completion compared to a rescue approach.

INTRODUCTION

Although pegylated interferon-alpha may provide a sustained viral response from chronic hepatitis C infection[^1^][^2^],...
this lengthy regimen is challenging to tolerate. Depressive symptoms, one of the more difficult side effects, can lead to discontinuation. Discontinuation rates for factors other than antiviral non-response range from 10% in well-conducted clinical trials[1,2] to 30% or more in clinical settings[3]. If depressive symptoms emerge, they must be clinically managed, including suspension of antiviral treatment as a last resort. Direct-acting antiviral agents may eventually supplant interferon-alpha/ribavirin regimens as standard of care[4], but interferon-alpha-based regimens have recently been re-affirmed as standards of care[5,6].

To reduce the threat of treatment-related depression, the idea of prophylactic depression treatment emerged[7]: when beginning interferon-alpha (and ribavirin) treatment, the patient would be started on an antidepressant with the goal of preventing, or attenuating, depressive symptoms. Initial case studies and case series noted success of this strategy. For example, antiviral treatment was restarted in a cohort of eight chronic hepatitis C patients who previously had discontinued due to emergent depressive episodes; all eight were able to fully complete the second course of treatment[8]. A precedent for this strategy was noting the success of antidepressant prophylaxis for interferon-alpha treatment of malignant melanoma[9,10].

Compared to prophylaxis, traditional practice can be termed “rescue” when depressive symptoms emerge in a patient undergoing antiviral treatment, depression treatment is quickly initiated so that those symptoms can be managed. The advantage to the prophylactic strategy is that depression and the threat of discontinuation can be avoided; the advantage to the rescue strategy is that patients are not unnecessarily treated, and so are not experiencing the additional treatment burden and side effects. Antidepressants may have quite adverse side effects in some patients, including retinal or gastroenterological bleeding[8,10]. Thus, clinicians are faced with a challenging clinical management strategy where risks and benefits must be considered.

Can prophylactic antidepressant treatment boost interferon-alpha treatment completion in patients with chronic hepatitis C virus (HCV)? No study has prospectively answered this question. This review has been conducted to discern an answer by reviewing antiviral therapy discontinuation data reported in trials evaluating the efficacy of antidepressant prophylaxis for managing depression. This review is presented in order to enhance the evidence available for clinical decision-making.

LITERATURE SEARCH

A Pubmed literature search was designed to discover trials that might have the data necessary to assess relative treatment completion between prophylaxis arms and control arms. A set of search terms was developed to capture studies relevant to hepatitis C. This included: “hepatitis”, “HCV”, “Hep C”, “Hep-C” and “chronic hepatitis C”. This was crossed with each of two other sets. The first was a set to capture depression-related studies: “depression”, “depressed”, “depressive”, “psychiatric”, “mental”. The other was a set to capture prophylactic strategies: “prophylaxis”, “prophylactic” or “prevention”.

From this search, all study titles would be reviewed to detect promising abstracts. All promising abstracts would be read, and likely studies would be pulled and assessed for necessary information. References of those studies would be checked manually.

The necessary information for selection into this review was established as the following: patients with chronic hepatitis C who were candidates for interferon-alpha treatment (whether including ribavirin or not, as this treatment strategy emerged as the prophylactic strategy emerged); recognized treatment regimen (i.e., interferon-alpha with ribavirin); no concurrent treatment such as for human immunodeficiency virus, since symptoms and treatment side effects would be significant confounders; at least two study arms where one included prophylactic treatment with an antidepressant, whether open-label or blinded, and the other is a control arm, whether placebo-controlled or not; sustained treatment of at least 8 wk in order to observe emergence of depressive symptoms from interferon-alpha and assess differential depression response between arms; and data on the numbers of patients in each arm that discontinued, or were lost to follow-up, for reasons other than medical side effects (thrombocytopenia, etc.) or non-response to antiviral therapy. Thus, the discontinuation group of focus would be those who medically could have completed treatment but discontinued for a reason other than a medical reason. To the degree that discontinuation reasons, such as psychiatric side effects, would be specifically reported, these would be tabulated and compared between the intervention-arm participants and the control-arm participants. The reporting of discontinuation for psychiatric reasons, specifically, was thus not an inclusion criterion.

For each eligible study, the number of patients discontinuing would be noted for each of the arms of the study. A descriptive analysis would be developed based on those results. The goal would be to describe the degree, if any, that antiviral treatment completion might be superior for the prophylactic strategy, compared side-by-side with the rescue strategy. Since the data sources for this study consisted of previously-published research studies, ethics approval for this narrative review was not sought from an institutional review board.

SEARCH RESULTS

For the “prophylaxis” search term set, “preventive” was soon discovered as a synonym, so this was added to that set. The “prophylaxis” set returned 1302661 abstracts; the “hepatitis C” set returned 184063 abstracts; and the “depression” set returned 869174 abstracts. The intersection of these three sets returned 419 abstracts. Titles of all were reviewed, leading to a set of 38 abstracts to review. This led to a set of 12 studies[8,12-23] in which the prophylactic strategy was evaluated, and discontinua-
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Table 1  Study characteristics and discontinuation data: Antidepressant prophylaxis for interferon-alpha treatment of hepatitis C virus

| Study                | Leading exclusion criteria                                                                 | Prophylactic intervention | Medication run-in period | Randomized: | Blinded: | Follow-up point, in wk | Discontinued/Total in Arm: | Prophylaxis | Rescue |
|----------------------|---------------------------------------------------------------------------------------------|---------------------------|--------------------------|-------------|----------|------------------------|---------------------------|-------------|--------|
| Schaefer et al[24]   | Psychiatric history, interferon treatment                                                   | Escitalopram              | 2 wk                     | Yes/No      | Yes/No   | 24/48                  | 2/90/3 91                  |             |        |
| Klein et al[20], 14/106 | Active psychiatric disorder in the recent six months                                       | Citalopram               | 3 wk                     | Yes         | Yes      | 12                     | 3/29/1 30                 |             |        |
| Klein et al[19], 14/106 | Current Axis I disorder or current psychiatric prescription                                | Escitalopram             | 2 wk                     | Yes         | Yes      | 24                     | 2/34/2 37                 |             |        |
| de Kreeg et al[16]   | Recent 3 mo psychiatric disorder                                                           | Citalopram               | 2 wk                     | Yes         | Yes      | 24                     | N/A A^3/ N/A A^3          |             |        |
| Morasco et al[18]    | Active psychiatric disorder in the recent two months                                       | Escitalopram             | 2 wk                     | Yes         | Yes      | 24                     | 4/51/6 48                 |             |        |
| Liu et al[17]        | Alcohol use during treatment                                                               | Specific antidepressants | not reported             | No          | No       | 24/48                  | 11/23/2 25               |             |        |
| Díez-Quevedo et al[20] | Individual, family, and marriage counseling                                                | N/A                      | Yes                      | No          | 24       | 14/106: 9/106 for lack of compliance, 5/ for psychiatric reasons | 28/105: 11/105 for lack of compliance, 17/105 for psychiatric reasons |
| Neri et al[19]       | Substantial psychiatric history, interferon treatment                                       | Escitalopram             | 2 wk                     | Yes         | Yes      | 24                     | 2/10/No control group     |             |        |
| Gleason et al[23]    | Depression not yet in remission                                                           | Escitalopram             | 4 wk                     | N/A         | N/A      | 24/48                  | 2/10/No control group     |             |        |
| Morasco et al[15]    | Active psychiatric disorder in recent six months                                           | Citalopram               | 4 wk                     | Yes         | Yes      | 24                     | 3/13/3 15                |             |        |
| Raison et al[22]     | Psychiatric disorder or prescription within recent six months                              | Paroxetine               | 2 wk                     | Yes         | Yes      | 24                     | 0/18/6 18                |             |        |
| Kraus et al[16]      | Active substance abuse                                                                    | Paroxetine or citalopram | 3 wk                     | No          | 0/8      | Not reported for control group of 9 0/11 |                     |
| Schaefer et al[24]   | Current or recent psychiatric diagnosis or prescription                                     | Citalopram               | 2 wk                     | N/A         | N/A      | 24                     | 0/14/0/11               |             |        |
| Totals: 47/396       |                                                                                           |                           |                          |             |          | 45/380                 |                          |             |        |

^1If 24/48, then treatment period accorded to interferon alpha regimen according to genotype, typically 24 wk for genotypes 2 and 3, and 48 wk for genotypes 1 and 4; ^2Denominator is total, including those lost to follow-up, who could have dropped out due to psychiatric reasons, and excludes those without this possibility, which would include the following: non-response to antiviral therapy, drop-out after randomization but before beginning antiviral therapy, or medical adverse events such as thrombocytopenia; ^3Three of 39 altogether discontinued antiviral therapy, but study report did not distinguish between active treatment and placebo for medical or other discontinuations; ^42008 study was a trial design report, and 2012 was poster of initial results recently presented at a conference; ^5Retrospective observational chart review study; analysis limited to the two of four study arms that constitute a prophylaxis vs rescue comparison; 19 of the 23 in the prophylaxis arm were already taking antidepressants and the remaining 3 were started prophylactically before starting antiviral therapy.

These studies are listed, with relevant study characteristics, in Table 1. All but one were prospective trials; one was a retrospective chart review study that composed a cohort of patients who were taking an antidepressant before the initiation of interferon-alpha treatment, and composed a control group of patients who required some kind of psychiatric treatment during interferon-alpha treatment. For the sake of completeness, this chart review study was included. One of the 12 studies (Gleason et al[23], 2007), among the first chronologically, did not have a control group; this study simply investigated treatment completion when a prophylactic strategy was trialed. This was included for completeness. For one study, the manuscript reporting the preliminary study design was available, and results have just recently been presented as a poster at a scientific conference; it is assumed that a more complete analysis will be forthcoming. For the sake of completeness, results based on this conference poster were included.

Clinical Interventions

All studies were conducted in the era of prescribing ribavirin along with interferon-alpha. Nearly all were conducted in the era of pegylated interferon, with the exception of some of the earlier-initiated participants in the Morasco et al[21] (2007) and Raison et al[22] (2007) studies. Likewise, antidepressant dosages were normative, with typical strategies for increasing or augmenting dosage when clinically indicated, and typical medication switching strategies when clinically indicated. All studies used antidepressants from the selective serotonin re-uptake inhibitor class, including paroxetine (one study), paroxetine or citalopram (one study), citalopram (five studies), and escitalopram (four studies). This usage followed the pattern of Food and Drug Administration approval and clinical
adopted of these drugs, with paroxetine favored in earlier studies, citalopram favored in the studies conducted in the middle of this time span, and escitalopram favored in later studies. A range of strategies were used to assess depression level before and during treatment. These generally included: standardized clinical interview, clinical interview, a depression questionnaire, or combination. In some studies, patients could be started on antiviral therapy even if some level of depressive symptoms was present.

Clinical outcomes

The overwhelming majority of patients were able to complete interferon-alpha treatment. Sustained viral response

results were in line with other well-managed intervention studies using interferon-alpha and ribavirin (e.g., approximately 40% sustained viral response for those with genotype 1, approximately 75% for those with genotypes 2 or 3). Some patients failed to show a treatment response, and so interferon-alpha was discontinued due to lack of response. Some patients had treatment-related adverse events, such as thrombocytopenia, requiring discontinuation of therapy. To the degree that these data were available, the current study did not include these patients in the denominator at risk of discontinuing due to psychiatric difficulties, since they had discontinued due to medical reasons. Patients who were lost to follow-up or discontinued for other preference or discretionary reasons, or for unidentified reasons, were included in the numbers of patients who discontinued treatment for some reason other than antiviral non-response or medical side effect. This strategy was chosen because it can be challenging, especially from limited data included in published studies, to determine the leading reason for discontinuation or loss to follow-up, and the clinical question is whether prophylaxis boosts study completion.

Generally, providing antidepressant treatment resulted in amelioration of depressive symptoms. For the groups receiving antidepressant treatment prophylactically, average levels of depressive symptoms, or the portion of patients with an emergent depressive disorder, were lower in those receiving prophylactic treatment by rescue treatment. Generally, problems with depression were worse for those at baseline with any depressive disorder history, or with higher initial depression severity.

Despite the clinical efficacy of antidepressant prophylaxis in controlling depressive symptomatology, there seemed to be no indication that the prophylactic strategy boosted treatment completion rates compared to the rescue strategy. Table 1 presents these data by study, including a summation of the total number of patients in the denominator, at risk for discontinuation, for both prophylactic and rescue arms, and the number for both arms that discontinued therapy. Of 396 patients in the prophylaxis arms altogether, who did not discontinue due to medical adverse events or clinical non-response, 47 (11.9%) discontinued interferon treatment before a recognized stopping point (e.g., 24 or 48 wk); of 380 patients in the rescue arms, 45 (11.8%) discontinued interferon treatment. There was no overall statistical difference when tested by Chi-Squared test with Yates’ correction ($\chi^2 = 0.00, P = 0.99$).

One study (Raison 2007) seemed to yield a desired effect for prophylaxis: none of the 18 prophylaxis patients discontinued, while 6 of the 18 rescue patients discontinued. A review of this study in the context of other studies did not reveal any clear aspect of study design, measurement, or sampling that would indicate an explanation for this divergent result from the other, similar studies.

The Liu et al (2010) study had greater discontinuation in the prophylaxis arm, but the psychosocial intervention used in this study, close monitoring and various counseling modalities, and psychopharmacotherapy only in certain cases where this psychosocial intervention was not successful, was very different from the other studies. Aside from this differential in discontinuation, the psychosocial intervention used in the Liu et al (2010) study otherwise was successful in managing psychiatric symptoms, and doing so with less dependence on psychopharmacotherapy, compared to the usual care arm with rescue psychopharmacology. In this Liu study, with a psychosocial strategy for prophylaxis rather than psychopharmacotherapy, the number of patients experiencing severe psychiatric symptoms was lower in the intervention group, with five meeting this criterion, vs 17 in the control group. Psychiatric symptomatology at less severe levels, likewise, was less frequent for the intervention arm compared to the control arm, with only six of the intervention patients eventually receiving antidepressant treatment compared to 19 in the control arm.

There were nine studies with data that permitted a Fisher’s Exact Test to test whether the discontinuation rate differed between prophylaxis arm and rescue arm. Of these nine, only four had results that were statistically significant. Three modestly favored prophylaxis. These were: Diez-Quevedo et al (2010) (7.8% discontinuation in prophylaxis arm, 12.5% rescue arm, Fisher’s $P = 0.02$), Neri et al (2010) (8.5% discontinuation in prophylaxis arm, 10.5% discontinuation in rescue arm, Fisher’s $P = 0.02$), and Raison et al (2007) (0.0% prophylaxis arm, 33.3% rescue arm, Fisher’s $P = 0.02$). The one study favoring rescue was Liu et al (2010) (47.8% discontinuation in prophylaxis arm, 8.0% discontinuation in rescue arm, Fisher’s $P = 0.02$). With five studies having no statistical difference in discontinuation, three favoring prophylaxis by varying portions, and one favoring rescue by a strong portion, there seems to be no consistent pattern favoring either strategy.

Since these studies were focused upon the presence and severity of depressive symptoms, but not on reasons for failure to complete a full course of therapy, reasons for not completing therapy were not systematically reported, and those reporting did not use consistent criteria. For those that did report, the stated reasons for discontinuation are listed in Table 2. Predominant reasons for not completing therapy included: lost to follow-up, psychiatric side effects, and non-adherence. These reasons are likely quite overlapping, such as a person...
choosing to fail to continue in treatment due to psychiatric symptoms.

**DISCUSSION**

Emergence of depressive symptoms is a challenging side effect when treating chronic hepatitis C with interferon-alpha. Rates of depression may be as high as 30% or more. It has been established that monitoring patients for the emergence of depression, and rescuing those in whom depression emerges, is a successful strategy for limiting treatment discontinuation or poor adherence. Because of this high incidence of treatment-related depression, the idea of prescribing an antidepressant prophylactically to all patients at the initiation of antiviral therapy is attractive. This search revealed 12 studies that have evaluated the benefits of prophylactic treatment. From these studies, it is clear that prophylactic treatment serves to reduce the emergence of depression, and serves to manage the level of depressive symptomatology.

This review was undertaken to investigate the degree that the prophylactic strategy might boost treatment completion. There is no clear indication that the prophylactic strategy generally serves to boost treatment completion, compared to a monitor-and-rescue strategy. Where noted, nearly all patients in the rescue arms were successfully rescued from the emergence of depression. Review of study parameters does not suggest any treatment strategy or patient profile where prophylaxis yields a boost in treatment completion.

Advantages to prophylaxis are the superior management of depression during treatment in some portion of patients. This advantage needs to be weighed against the negatives of this strategy, which include the increased treatment burden on the patient, increased cost, and the risk of adverse events from the antidepressant. Two of the reviewed studies indicate some likely applications for prophylaxis. The study by Schaefer et al.[18] (2005) demonstrated lower rates of treatment-related depression in the prophylactically treated arm, compared to the arm with no prophylaxis, in a cohort of patients with chronic hepatitis C who also had a history of a mental disorder (predominantly affective and dependence disorders) but with no active symptomatology and not currently receiving any psychiatric medication. The Kraus et al.[19] (2005) study demonstrated successful interferon-alpha retreatment with antidepressant prophylaxis for a cohort of patients who had previously discontinued interferon-alpha treatment due to the emergence of depressive symptoms, while the control arm experienced, on average, even higher depressive symptom levels in the second attempt at interferon-alpha treatment (possibly due to the use, for all, of pegylated interferon-alpha in the second but not first treatment attempt). So, certain subgroups with recognized psychiatric difficulties may benefit from antidepressant prophylaxis.

While psychopharmacology is effective for managing depression in interferon-alpha treatment of hepatitis C, it is interesting to note the positive results of the Liu study, with a psychosocial intervention including individual counseling, family counseling, and couples counseling. The exact design of this intervention was not reported, such as how counseling needs were discovered, or data on the number of sessions delivered, or the specific clinical issues addressed, or whether any component included comprehensive chronic illness management training (disease education, treatment education, stress management, physician-patient communication skills, etc.), which has been shown to improve treatment adherence along with health-related quality of life.

Why didn’t the prophylaxis approach have superior treatment completion, along with superior depression management, compared to rescue approach? It is possible that, in these trials, the rescue strategy worked as well as prophylaxis because clinical trials often have clinical management practices (answering patient questions, establishing clear lines of communication, systematic symptom monitoring, recruitment of motivated patients) that is stronger than usual care. If this is the case, then those delivering interferon-alpha treatment for chronic hepatitis C should be sure to parallel the symptom monitoring strategy of these trials. The monitoring of depression is a topic that has already been covered well in the literature concerning antiviral therapy, and has long been incorporated into treatment guidelines. The results of the Neri et al.[18] (2010) study support this possibility: strong psychosocial monitoring led to better affective symptom control, with only a small portion of that advantage due to the use of antidepressants. At the same time, it is valuable to note that, in the Liu et al.[19] (2005) study, interferon-alpha treatment conclusion or discontinuation led to a reduction in the emergent depressive symptom levels seen, leading the authors to conclude that “depression was specifically related to IFN therapy”.

One indirect benefit of antidepressant treatment may be the management of treatment side effects other than psychiatric side effects. Raison et al.[20] (2007) found stronger completion rates in the prophylaxis arm, and this was noted as being related to lower antiviral side effect difficulties. The study by Diez-Quevedo et al.[21] (2010) also noted lower levels of antiviral side effects in those receiving antidepressants. Antidepressants are used in a range of clinical indications beyond depression, such as management of pain and management of fibromyalgia symp-
In antiviral therapy, antidepressants may somehow reduce a range of symptoms. This could explain an unusual finding regarding depression in a larger hepatitis C study\textsuperscript{24} that used a rescue strategy for emergent depression: while depression emerged for 90 patients in this study of nearly 400, discontinuation rates were lower for those patients (6%) than for those in whom no depression emerged (15%). The antidepressant intervention, or the related social support experienced in the course of clinical response, may have served to ameliorate the experience of treatment side effects. Data were not sufficient in the studies reviewed here to investigate more fully the possibility that antidepressant treatment in antiviral treatment may ameliorate antiviral-related side effects.

Another treatment characteristic suggesting that prophylaxis has limited clinical benefit was the necessity of monitoring and rescuing patients in the prophylaxis group, as well as the rescue group. In the de Kreeg et al\textsuperscript{28} (2011) study, with 40 patients in the escitalopram group and 39 in the placebo group, four in the prophylaxis group needed rescue (increase or augmentation of dose, or new medication) while seven patients in the placebo group needed rescue depression treatment. In the Schaefer et al\textsuperscript{29} (2012) study, three in the prophylaxis group needed rescue by another antidepressant, while 16 in the rescue arm required rescue. In the Morasco et al\textsuperscript{30} (2010) study, approximately 30% in each arm had to have medication dosage adjusted, with some of those in the prophylaxis arm entering “rescue” treatment. This need to monitor and adjust pharmacotherapy is a limit to the treatment efficiency to be gained by prophylaxis; prophylaxis does not reduce the necessity of monitoring patients for the emergence of depression symptoms, and so does not greatly lighten the task of clinical care required to manage depression.

Because the influences of cytokines upon the central nervous system are quite varied, it is not quite clear how interferon-alpha causes depression in some patients. Pro-inflammatory cytokines can experimentally induce “sickness behavior” in non-human animals. It is hypothesized that this malaise might serve a valuable function: when the body needs to fight off infection, it is advantageous to have a healing period of increased sleep, lower activity level, and lower appetite; pro-inflammatory cytokines promote inflammatory responses, and also may simultaneously be registered in the brain, leading to the coincident sickness behavior\textsuperscript{31}. Research in humans has revealed that interferon-alpha has an array of effects in the central nervous system, and elevated cytokine activity, especially tumor-necrosis factor-alpha and interleukin-6 can be noted in some portion of cases of major depression\textsuperscript{26,27}. Further, serotonin-acting antidepressants have an effect upon tumor-necrosis factor-alpha and interleukin-6, as well as other inflammatory markers\textsuperscript{29}.

Providers should be clear about desired purpose when considering prophylactic antidepressant for hepatitis C patients about to begin antiviral therapy. Antidepressant prophylaxis does not seem to boost treatment completion, so other goals, such as managing depression, should be clarified when considering the strengths and weaknesses of this strategy. Discontinuation of interferon-alpha for chronic hepatitis C is a great treatment challenge, and anything that interferes with completion of treatment should be well investigated.

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