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Can antidepressants prevent interferon-alpha-induced depression? A review of the literature

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Abstract

Objective: To review the literature about the efficacy of antidepressant prophylaxis during interferon-alpha (IFN-α) therapy.
Method: We have performed a database search in PUBMED and ISI Web of Knowledge (1980–August 2009) for the available literature. The keywords "prevention" or "prophylaxis", and "depression", and "interferon", and "antidepressant" or "antidepressive agents" were used.
Results: The six eligible studies comprise three randomized controlled trials, two in hepatitis C virus (HCV) patients and one in individuals with melanoma, and three open-label studies with HCV patients. The results of the randomized controlled trials suggest that antidepressant prophylaxis may blunt the magnitude of depressive symptoms in HCV patients and raise the rates of treatment completion. In melanoma patients, this preventive strategy may reduce the incidence of depression during IFN-α treatment. In addition, the open-label studies with HCV patients suggest that this strategy may reduce the onset of major depression in specific samples (current psychiatric diagnosis, major depression in remission, past history of IFN-α-induced depression) on IFN-α (re-)treatment.
Conclusions: In the face of so few trials about the usefulness of prophylaxis with antidepressants before IFN-α treatment, there is not enough information to sufficiently and widely support this strategy to prevent depression. However, this approach may, nonetheless, bring some beneficial outcomes, if applied to specific patient groups.

Keywords: Major depression; Interferon-alpha; Prevention; Antidepressant; Review

1. Introduction

Interferon-alpha (IFN-α), conventional or pegylated (PEG), in combination with ribavirin (RBV), constitutes the only Food and Drug Administration-approved treatment for chronic hepatitis C virus (HCV) infection, a disease that affects over 170 million individuals worldwide [1–5]. Moreover, IFN-α is the current approved adjuvant treatment for melanoma [6,7].

Despite its potential therapeutic benefits, administration of IFN-α frequently prompts the appearance of neuropsychiatric symptoms, e.g., depressed mood, anxiety, psychosis, suicidal behavior, and acute dystonia, as well as neurovegetative and somatic symptoms, e.g., anorexia, psychomotor slowing, and altered sleep [3,8–10]. Clinical studies have shown that approximately 30–45% of patients receiving IFN-α develop a major depression episode (MDE) that may lead to severe outcomes, such as suicidal behavior during the course of the therapy [1,3]. Additionally, IFN-α-induced MDE limits IFN-α therapeutic potential by compromising compliance, and leading to dose reduction or interruption of the therapy [1]. However, in spite of the IFN-α-related side-effects cited, this cytokine represents an opportunity for

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improvement or cure of severe diseases, such as chronic hepatitis C and melanoma [11–15].

Although some antidepressants (ADs) seem to be efficacious in treating the IFN-α- induced MDE [7,16,17], prophylactic interventions proposed to minimize the challenges and complications of IFN-α-induced depression have demonstrated contradictory results [7,10,16].

Therefore, we have conducted a comprehensive review of the literature to evaluate the efficacy of AD usage to prevent an MDE during IFN-α therapy, for any therapeutic purpose, and critically discussed some important issues concerning this preventive strategy.

2. Methods

2.1. Study design

Our aim was to identify all clinical trials evaluating the efficacy of AD prophylaxis before initiating IFN-α therapy. Studies were selected, in our review, in which patients were treated for any approved indication of IFN-α. Moreover, additional inclusion criteria were: administration of AD at least 2 weeks before initiating IFN-α in monotherapy or combined with another agent directly related to the treatment of the target disease (e.g., RBV); maintenance of AD and study duration of at least 12 weeks; onset or relapse of an MDE as the primary outcome; and use of a standard psychiatric diagnostic instrument and/or severity depression scales. Case reports, depression treatment studies and review articles were excluded.

2.2. Literature search

Two investigators (A.G.A. and L.C.Q.) independently searched PUBMED and ISI Web of Knowledge databases, from 1980 to August 2009, for the published literature on the use of ADs for prevention of depression during IFN-α treatment. The keywords were "prevention" or "prophylaxis", and "depression", and "interferon", and "antidepressant" or "antidepressive agents." The search was limited to clinical trials and to articles published in English, but not to the therapeutic purpose of IFN-α treatment. Bibliographies of all relevant studies and recent review articles were scanned to identify subsequent citations.

2.3. Data extraction

Data were extracted by two independent observers (A.G. A. and L.C.Q.) using standardized forms. Recorded data included the target disease of IFN-α treatment, instruments and scales used, ADs administered, number of patients, incidence of depression during the treatment, and the impact of pre-administration of ADs on depression severity.

3. Results

The search strategy generated 30 studies, 27 of which published in English, which were screened for relevance related to the topic. These studies included eight review articles, one design of a study yet to be performed — related to depression prevention in HIV–HCV-infected patients, five experimental studies, one study evaluating compliance to IFN-α therapy in HCV patients, one biostatistical study, one letter to the editor commenting a randomized controlled clinical trial (RCT), one pharmacogenetic study and one case report related to depression prevention in a melanoma patient on IFN-α treatment. Two clinical trials were excluded: one therapeutic study evaluating the response of IFN-α-induced depression to citalopram and another analyzing paroxetine responsiveness of symptom dimensions with a sample already investigated in a previous RCT. A total of six clinical trials fulfilled the criteria for consideration in this review, comprising 197 participants. The characteristics of these clinical trials are summarized in Table 1.

Among these clinical studies, three RCTs [7,10,19] were identified. A total of 134 participants were enrolled in these three studies, and Table 2 shows their outcome data.

Morasco et al. [7], in the first RCT evaluating the utility of an AD medication in the prevention of IFN-α-induced depression in HCV patients, demonstrated that paroxetine treatment did not result in statistically different rates of MDE when compared with those of the placebo administration (see Table 2). In this study, AD pre-treatment did not delay the onset of clinically significant depressive symptoms (P=.35), nor did it impact on IFN-α treatment completion rates (P=.62). However, HCV patients assigned to paroxetine were more likely than patients assigned to placebo to achieve a sustained virological response (SVR) (P=.019).

Table 1
Summary of clinical trials related to IFN-α treatment and prevention of depression

First author, year	*n*	Study design	Main evaluation	Disease	Antidepressant
Musselman, 2001 [19]	40	RCT	Depression prevention	Melanoma	Paroxetine
Schaefer, 2005 [20]	36	OLT	Depression prevention	HCV	Citalopram
Kraus, 2005 [21]	17	OLT	Preventing IFN-α-induced depression recurrence	HCV	Paroxetine/Citalopram
Gleason, 2007 [18]	10	OLT	Preventing depression relapse	HCV	Escitalopram
Raison, 2007 [10]	61	RCT	Depression prevention	HCV	Paroxetine
Morasco, 2007 [7]	33	RCT	Depression prevention	HCV	Paroxetine

RCT, randomized controlled clinical trial; OLT, open-label trial.

Table 2
Summary of randomized controlled trials evaluating antidepressant prophylaxis during IFN-α treatment

First author, year	Disease	Diagnostic instrument; depression severity instrument	No. of patients (% male)		N (%) of patients developing MDE		Mean highest HAM-D score during AD prophylaxis	
			AD group	PLC group	AD group	PLC group	AD group	PLC group
Musselman, 2001 [19]	Melanoma	*DSM-IV*; HAM-D, CDS	20 (50)	20 (50)	11 *P*=.04*	45	8.4 *P* < .001*	15.2
Morasco, 2007 [7]	HCV	SCID I; HAM-D	14 (100)	19 (100)	31.6 *P*=.56	35.7	13.2 *P* > .05	15.5
Raison, 2007 [10]	HCV	SCID I; MADRS	33 (60.6)	28 (53.6)	13 *P*=.71	20.7	– –	–

PLC, Placebo; SCID, Structured Clinical Interview for *DSM-IV*; CDS, Carroll Depression Scale.
* Statistically significant difference, *P*<.05.

Raison et al. [10] also found that HCV patients, randomized to the paroxetine group, did not display a reduced incidence of MDE during IFN-α treatment (see Table 2) compared with those randomized to placebo. However, these individuals displayed a significantly lower rate of study discontinuation after initiation of therapy (*P*=.03). Additionally, according to the cutoff scores of the Montgomery Asberg Depression Rating Scale (MADRS), the percentage of patients meeting the criteria for mild, moderate or severe depression at any point during IFN-α therapy was significantly lower in paroxetine- vs. placebo-treated subjects (*P*=.02). As a continuous variable, MADRS scores in the paroxetine group showed significantly lower numbers at 16 and 20 weeks of IFN-α treatment (*P*<.05).

In the same study, a past depression history was not associated with MADRS scores during IFN-α treatment. On the other hand, baseline MADRS scores exhibited a significant main effect on depression symptom severity (*P*<.0001) and, when these baseline scores were above the median, those randomized to the AD group demonstrated significantly reduced depressive symptoms, more pronounced at Weeks 16 and 20 when compared with those of the placebo group (*P*<.01) [10].

On the other hand, another study showed that melanoma patients were significantly benefitted from pre-administration of paroxetine not only in terms of depression severity, but also in terms of the incidence of depression during IFN-α treatment, which was significantly reduced (see Table 2). The same study reported that by Week 12 of therapy, the scores on the Hamilton Depression Rating Scale (HAM-D) among individuals in the paroxetine group were almost 50% lower than among those in the placebo group (*P*=.01). The AD treatment also significantly decreased the likelihood of IFN-α therapy discontinuation motivated by severe depression (*P*=.03) [19].

Schaefer et al. [20] conducted an open-label study to evaluate the efficacy of citalopram to prevent depression emerging during the IFN-α therapy in HCV patients with psychiatric disorders (Group A) and used two HCV-infected control groups: one with mental disorders (Group B) and another without a psychiatric risk factor (Group C). During the 6-month period of IFN-α treatment, major depression was diagnosed by a clinical assessment consistent with the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) criteria in 15 (42%) out of the 36 patients. They also found that pre-treatment of psychiatric patients with the ADs significantly reduced the incidence of major depression during the first 6 months of antiviral treatment as compared to the control groups (Group A 14% vs. 64% and 55% in Groups B and C, respectively; log-rank test 6.89; *df*=2; *P*=.032).

Kraus et al. [21] performed an open-label trial aiming to prevent depression recurrence during re-treatment of HCV individuals who had already developed an IFN-α-induced MDE in a previous trial. The control group was comprised of HCV patients who had failed to respond to a previous IFN-α treatment, but did not display significant depressive symptoms, and wished to be re-treated for chronic hepatitis C. Depression scores were significantly lower (*P*=.036) during IFN-α re-therapy with selective serotonin reuptake inhibitor (SSRI) prophylaxis. The control group subjects showed similar depression scores during first therapy and re-therapy (*P*>.05). None of the patients had to interrupt re-treatment prematurely due to psychiatric side-effects. Sustained virological response subsequent to antiviral re-treatment was observed in five of eight patients pretreated with paroxetine or citalopram.

Another open-label study aiming to prevent depression relapse was performed in HCV patients with a past history of *DSM-IV* major depressive disorder (non-related to IFN-α), currently in remission. Eligible individuals were started on escitalopram (10 mg/day) four weeks before initiation of PEG IFN-α-2a and RBV combination therapy, which was maintained during the entire course of the antiviral therapy. Throughout the course of the treatment, there were no statistically significant increases in mean depression scores compared to baseline (*P*=.568). Nine of 10 subjects (90%) maintained HAM-D of <17 (remission criteria) throughout the study. The authors suggested that AD pretreatment allowed these patients to complete the IFN-α treatment. Moreover, it was reported that the only subject that experienced a clinically significant return of depressive

symptoms during the study was adequately treated with an adjustment of the AD dose [18].

It is important to emphasize the lack of comments on the adverse effects of AD administration in three studies (Morasco et al. [7], Gleason et al. [18], Schaefer et al. [20]). While Raison et al. [10] show that dizziness was significantly more frequent in the paroxetine group, Kraus et al. [21] did not find differences in the side-effects presented by the AD group when compared to the non-AD group.

Finally, even though Musselman et al. [19] concluded that types of adverse events did not differ between groups, they cited that 3 out of 15 patients taking paroxetine had to be withdrawn from participation due to adverse effects. These authors also mention that after the study period, three patients using the AD presented retinal hemorrhages, including one with irreversible loss of vision, although they do not affirm that paroxetine was definitely the cause of the bleeding.

4. Discussion

This comprehensive review of the literature included six clinical trials evaluating the effect of AD administration before initiating IFN-α therapy on the prevention of MDE onset. Even though the RCTs agreed on the use of paroxetine, divergences regarding the clinical characteristics of the samples, study designs and the ADs used were identified in the other studies.

In addition, secondary outcomes derived from HCV studies, such as significantly lower rate of study discontinuation [10] and higher rate of SVR [7] in patients randomized to the AD group, were also found. It is reasonable to assume that HCV patients, who do not develop depressive symptoms, or have them alleviated by an AD treatment, are more likely to remain on IFN-α regular therapy and achieve an SVR [17]. However, a possible anti-inflammatory effect of ADs, which could negatively influence viral clearance during IFN-α treatment in HCV individuals, is also speculated [22].

Some relevant risk factors may explain the different response to AD pre-administration between melanoma and HCV-infected patients; higher IFN-α doses, intravenous administration and longer duration in melanoma treatment may have had an important impact on depression incidence outcomes and consequently on the magnitude of the response to AD prophylaxis [5,23]. In fact, the rates of a substance-induced MDE are higher in melanoma patients on IFN-α treatment (45–50%) [8,19], compared to HCV individuals (30%) [7]. Finally, the disease itself (melanoma or chronic hepatitis C) may represent an independent factor in the development of depression, turning IFN-α-induced depression in these cases into a different clinical phenomenon [7].

Additional important issue that must be addressed is the need for more accurate incidence rates of this substance-induced mood disorder. Most of the available studies in the literature evaluating the incidence of IFN-α-related depression found a wide range of estimates: 0–70% [3]. The variability can be attributed mainly to discrepant methodologies applied, such as diverse study designs, sample selection, diagnostic instruments and symptom scales [5]. Nevertheless, even in more homogenous studies, these depression rates can reach up to 45% in IFN-α-treated individuals [3]. These numbers are two to three times higher than the lifetime prevalence of MDE (16.6%), and at least five times higher than the 12-month prevalence of an MDE in the general population (6.7%) [24,25]. These findings suggest that either the instruments currently used are inadequate to access this particular kind of depression, consequently overestimating its incidence, or there is an underestimation of its importance in the clinical practice.

Another relevant point is that clinicians should exercise additional caution in using AD agents in individuals with general medical conditions. Indeed, even considering the evidence of such high incidence rates, the majority of IFN-α-treated patients do not develop an MDE, and therefore AD preventive strategies may unnecessarily expose many individuals to another medication and to the related adverse effects [2,18,26]. Furthermore, although the main pathophysiological hypothesis of IFN-α-induced depression involves the serotonergic pathway [5], other neurotransmitters, such as dopamine and glutamate, may be related to this substance-induced MDE. In this context, the search for new drugs to treat these patients [18,27], and preventive interventions with minimal potential for adverse effects, such as the psychological ones [28], are justified.

Nevertheless, we emphasize the importance of the study suggesting that prophylactic administration of ADs could be successfully used in a subgroup of patients having such stable comorbid psychiatric disorders as major depressive disorder and substance-use disorder, but with mild to moderate symptoms prior to IFN-α treatment [20]. These data confirm the recent findings that subclinical affective symptoms, regardless of a past psychiatric history [29,30], represent the main risk factor for the onset of psychiatric side effects during this therapy, and raise questions related to the importance of early recognition of affective symptoms in these patients [31,32]. Finally, pharmacogenetic studies attempting to better characterize a more vulnerable subgroup of HCV patients treated with IFN-α have been published with the aim of proposing more accurate preventive AD strategies [33–35].

5. Conclusions

Future larger-sampled studies targeting a better characterization of the risk factors associated to IFN-α-induced MDE, and identification of new biological markers are essential to obtain a more specific diagnosis and a more efficient prophylactic intervention.

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