

Psychiatric side effects of pegylated interferon- α and ribavirin therapy in Iranian patients with chronic hepatitis C: A meta-analysis

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Abstract. An estimated 185 million people worldwide are infected with hepatitis C virus (HCV). Combination therapy with pegylated interferon- α (peg IFN) and ribavirin is the first line of treatment against the psychiatric side effects, including mood disorders, anxiety and irritability. In the present study, all of the studies electronically published between 2000 and 2016 were retrieved using databases including Scopus, PubMed, Institute for Scientific Information, Science Direct and Google Scholar. All of the articles were independently evaluated by two reviewers and the results were compared, followed by removal of duplicate, irrelevant and re-published studies after reviewing. The studies were assessed based on the heterogeneity of their results using the Cochrane test and I² analysis. All groups included neuropsychiatric side effects, fatigue was reported at the highest rate in 60.41% [95% confidence interval (CI)=39.18-81.64%] and insomnia was reported at a lower rate in 16.28% of cases (95% CI=6.59-25.98%). In conclusion, the present meta-analysis indicated that treatment with peg IFN + ribavirin or interferon only is associated with a wide range of neuropsychiatric side effects, including fatigue, mood disorders, anxiety, irritability, emotional ability and agitation.

Introduction

An estimated 185 million individuals worldwide are infected with Hepatitis C virus (1,2). Most of the mortalities associated with hepatitis C virus infection are due to cirrhosis and liver cancer (3). Combination therapy with pegylated interferon- α (peg IFN) and ribavirin is the first line of treatment (4). On average, 55% of patients consistently used these drugs (5). peg IFN in combination with ribavirin is the currently recommended treatment for 70-80% of genotype 2 or 3 and is also used for 40-50% of genotype 1 patients with HCV infection, and conventional interferon were used for other patients (6,7). peg IFN and ribavirin are successful antiviral treatment for numerous adverse effects, including fatigue, mood disorders, anxiety, irritability, emotional lability, agitation, apathy, anhedonia, anorexia, retardation, sleep disturbance, sexual dysfunction and cognitive deficits have been reported during and after the treatment of hepatitis C (8-10). Various studies have reported psychiatric side effects in ~84.5% of patients during treatment with peg IFN and in 42.6% of patients at 6 months after completion of treatment (7,11). In terms of psychiatric side effects, a relatively large body of literature documents high rates of psychiatric symptoms, the definition of which varies between studies, but all of them indicated that IFN induced psychiatric side effects ranging from 30-70% for depression, 39-80% for fatigue, 18-45% for sleep disturbances, 16-50% for irritability, 11-45% for anxiety, 0.0-3.2% for mania, 0.0-0.6% for psychosis, 3.5-10% for suicidal ideation and 0.0-0.2% for suicidal attempts. Previous studies have demonstrated that non-specific symptoms occur early and that certain psychiatric side effects may occur following the onset of therapy; most of these events occur after 3 weeks (12,13). These side effects were evaluated in patients treated with peg IFN and ribavirin in order to determine whether it is reasonable to reduce these effects by replacing those drugs. The present meta-analysis study assessed the psychiatric side

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effects of peg IFN and ribavirin in Iranian patients with chronic hepatitis C infection.

Materials and methods

Data source. In the present study, all of the studies published in electronic format from January 2000 up to December 2016 were included. Articles were searched using various international and Persian databases, including Scopus, PubMed, Institute for Scientific Information, Science Direct, Google Scholar, Magiran and SID (sid.ir). The search strategy was performed using the following major key words: 'Prevalence', 'HCV', 'Iran', 'psychiatry', 'ribavirin' and 'interferon'. 'AND'/'OR' operators were used to identify the articles, e.g. (interferon alpha OR pegylated interferon) AND (HCV OR Hepatitis C virus OR hepatitis C) AND (Iran OR Islamic Republic of Iran). In addition, all of the studies with a different aim to the present study were removed using the 'NOT' operator. For increasing the sensitivity of the present study, the references of retrieved articles were also considered. Two reviewers performed random searches in order to retrieve all of the relevant studies.

Study selection

Retrieval of articles. During the advanced search, all articles retrieved were collected, and duplicates and irrelevant articles were removed after reviewing the titles and abstracts. In addition, re-publication bias was prevented via excluding the any studies containing duplicated data. The articles were evaluated by two reviewers (T.M. and M.M.) independently and their results were compared with each other. Any disagreements were resolved by consultation with another researcher.

Quality assessment. In the present study, the quality of the selected articles was assessed with a STROBE checklist. This checklist comprised 22 questions based on the Strengthening the Reporting of Observational Studies in Epidemiology statement (14). These questions contain all of the aspects of the methodology, including data collection methods and tools, type of the study, definition of the variables, statistical analysis tests, study objectives, sample size estimation selection and study population. Each question was assigned to score one point. In this checklist, the minimum and maximum scores are 0 and 44, respectively. Based on the results of the quality assessment, studies were divided into three categories: Low (<15.5), average (15.5-29.5) and high quality (>30) and studies with low-quality scores were excluded from the final meta-analysis.

Inclusion criteria. All of the articles in English and Persian language with sufficient quality scores were included in meta-analysis if they met the following inclusion criteria: i) HCV patients using interferon or ribavirin or a combination of these two drugs during treatment; ii) the studies reported on psychiatric side effects among patients receiving IFN or ribavirin or their combination; iii) cross-sectional (descriptive-analytic) studies or cohort studies.

Exclusion criteria. The exclusion criteria applied in the present study were as follows: i) Case reports, author replies, animal

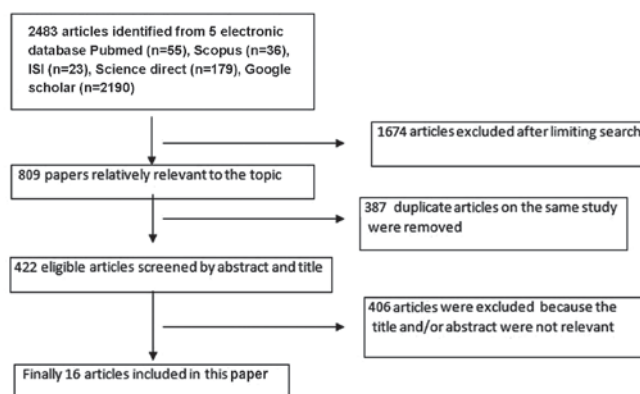


Figure 1. Flow diagram of the selection of studies included in the present meta-analysis.

studies, case series, reviews, commentaries, studies presented at conferences, studies that did not achieve the desired scores or that were unpublished; ii) duplicated studies and iii) studies reporting on psychiatric side effects among HCV patients that received other drugs.

Data extraction. The following information was extracted from the selected the articles: Title, author names, publication date, study location, population group, population size, age, study language, drug use and factors of psychiatric side effects. The information was recorded in an excel spreadsheet.

Statistical analysis. The standard error for primary studies was calculated with a binomial distribution formula: $(Se = \frac{\sqrt{P(1-P)}}{n})$. The degree of heterogeneity among the results was estimated by Cochrane's test (Q) and I^2 indexes. For detection of heterogeneity, a forest plot was used to indicate the mean frequency of occurrence and estimates with 95% confidence intervals (CIs; horizontal lines). Furthermore, publication biases were evaluated with Egger's test (with a significance level of <0.01). All statistical analyses were performed using the Stata SE, v.11 software (StataCorp LP, College Station, TX, USA).

Results

Study selection. In the initial search, 2,483 articles in the field of interest were identified. After the first limitation, 1,674 articles were preliminarily selected according to the search strategy. Subsequently, 387 duplicated articles on the same study were excluded and thereafter, 406 articles were removed due to having an irrelevant title and/or abstract. Finally, 16 eligible studies were retained (15-30), which were included in the meta-analysis (Fig. 1; Table I).

Quality evaluation. Among the selected studies, the prevalence of fatigue was reported in 5 articles comprising 802 patients and ranged from 21.6-74.0% (Table I). As there was heterogeneity between the results for fatigue, the random-effects model was used for assessment. By combining the results of these 5 studies, the frequency of fatigue was determined to be 60.41% (95% CI; 39.18-81.64%; Fig. 2; Table II).

In the present study, the prevalence of depression was reported in 6 articles comprising 706 patients and ranged

Table I. Characteristics of primary studies.

| First author, year | Sample size | age, years | Drug treatment | Duration (months) | Nerv. | Fat. | Dep. | Morning Ha. | Ha. | Dizzi. | Lethargy | Somm. | Anxiety | Exc. | Mood changes | Weak. | Irrit. | Ins. | An. | Score ^a | (Refs.) |
|-----------------------|-------------|------------|--------------------------|-------------------|-------|------|------|-------------|------|--------|----------|-------|---------|------|--------------|-------|--------|------|------|--------------------|---------|
| Namazee, 2012 | 100 | 42.0 | Interferon+ ribavirin | 48 | | 74 | 39 | | 38 | | | | | | | | 7 | | | 18 | (26) |
| Alavian, 2006 | 176 | 38.9 | Interferon+ ribavirin | 48 | 34.7 | 21.6 | | | | | | | | | | 0.5 | | | | 19 | (19) |
| Mirmomen, 2004 | 32 | 24.1 | Interferon | 48 | | | | | 16.3 | | | 22.5 | | 16.1 | 29 | 32.2 | | | | 17 | (24) |
| Alavian, 2004 | 52 | 38.5 | Interferon+ ribavirin | 48 | | | 5.8 | | | | | | | | | | | | | 18 | (16) |
| Alavian, 2010 | 367 | 30.0 | Interferon+ ribavirin | 48 | | 60 | 19 | | 36 | 20 | 21 | | 41 | | | | 24 | 26 | | 18 | (17) |
| Alavian, 2009 | 51 | 25.0 | Interferon | 48 | | 74 | | | | | | | | | | | | | | 20 | (18) |
| Bafandeh, 2007 | 118 | 37.47 | Interferon+ ribavirin | 24 | | | 15 | | | | | | | | | | | | | 16 | (20) |
| Forootan, 2005 | 97 | 35.1 | Interferon+ ribavirin | 12 | | | | | 13.6 | | | | | | 36 | | | 4.9 | 34 | 18 | (21) |
| Jabbari, 2010 | 108 | 39.0 | Interferon | 24 | | 73.5 | | | | | | | | | | | | | 66.2 | 17 | (22) |
| Mirmomen, 2003 | 29 | 25.24 | Interferon | 12 | | | | 3.4 | 10.3 | | | 13.7 | | | 27.5 | 17.2 | | | | 17 | (25) |
| Merat, 2004 | 37 | 30.1 | Interferon+ ribavirin | 48 | | | | | | | | | | | 31.4 | | | | | 16 | (23) |
| Zali, 2004 | 57 | 41 | Interferon+ ribavirin | 48 | | | | | | | | | | | 29.4 | | | | | 17 | (30) |
| Sandoughdaran, 2015 | 21 | 29.7 | Interferon+ ribavirin | 72 | | | 23.8 | | 71.4 | | | | | | | | | 9 | | 16 | (29) |
| Pouresmaeeli, 2015 | 247 | 39.2 | Interferon-2a+ ribavirin | | | | | | | | | | | | | | | 32.8 | 25.9 | 17 | (28) |
| Pouresmaeeli, 2015 | 42 | 37.7 | Interferon-2b+ ribavirin | | | | | | | | | | | | | | | 9.5 | 0 | 17 | (28) |
| Nasser Ebrahimi, 2004 | 23 | 45.43 | Interferon+ ribavirin | 48 | | | | | | | | | | | 48 | | | 26 | | 15 | (27) |
| Alavian, 2006 | 48 | 39.8 | Interferon+ ribavirin | | | | 6.25 | | | | | | | | | | | | | 19 | (15) |

^aStrobe checklist was used to score. Nerv., nervousness; Fat., fatigue; Dep., depression; Ha., headache; Diz., dizziness; Somm., Somnolence; Exc., excitability; Weak., weakness; Irrit., Irritability; Ins., insomnia; An., anorexia.

Table II. Results of meta-analysis and publication bias (Egger's test).

| Complication type | Number of studies | Sample size | Frequency | | Heterogeneity | | | Publication bias (Egger's test) | |
|-------------------|-------------------|-------------|-----------|-------------|---------------|-------|---------|---------------------------------|---------|
| | | | % | CI 95% | I-squared | Q | P-value | β | P-value |
| Fatigue | 5 | 802 | 60.41 | 39.18-81.62 | 97.6% | 166.9 | <0.001 | 8.9 | 0.460 |
| Depression | 6 | 706 | 17.31 | 8.88-25.75 | 91.5 | 42.8 | <0.001 | 1.2 | 0.743 |
| Headache | 6 | 646 | 29.61 | 16.44-42.77 | 92.2 | 63.9 | <0.001 | 0.1 | 0.979 |
| Mood disorders | 6 | 275 | 32.97 | 27.45-38.49 | 0 | 3.54 | 0.617 | 0.3 | 0.849 |
| Insomnia | 7 | 897 | 16.21 | 6.61-25.80 | 93.6 | 93.2 | <0.001 | 0.7 | 0.877 |
| Anorexia | 4 | 494 | 31.29 | 3.65-58.94 | 99.1 | 347.7 | <0.001 | 10.4 | 0.043 |

CI, confidence interval.

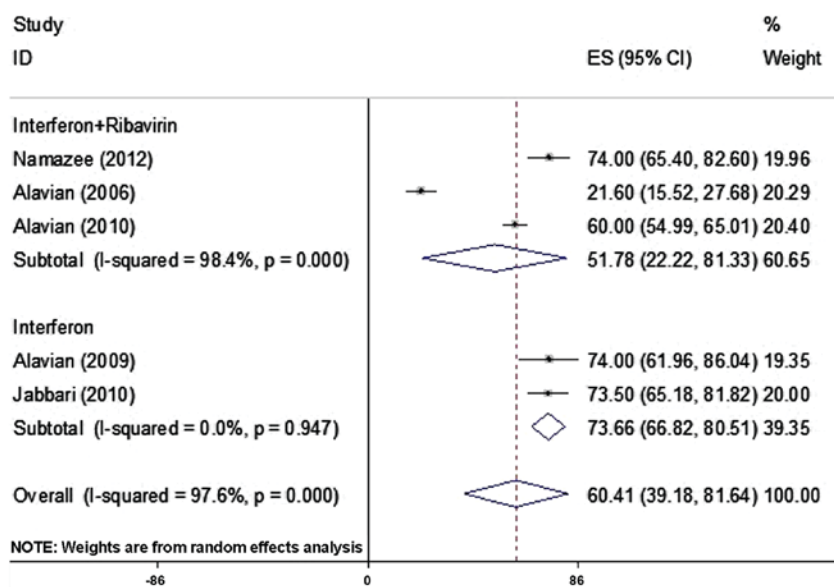


Figure 2. Forest plot of fatigue in primary studies. ES, effect size; CI, confidence interval.

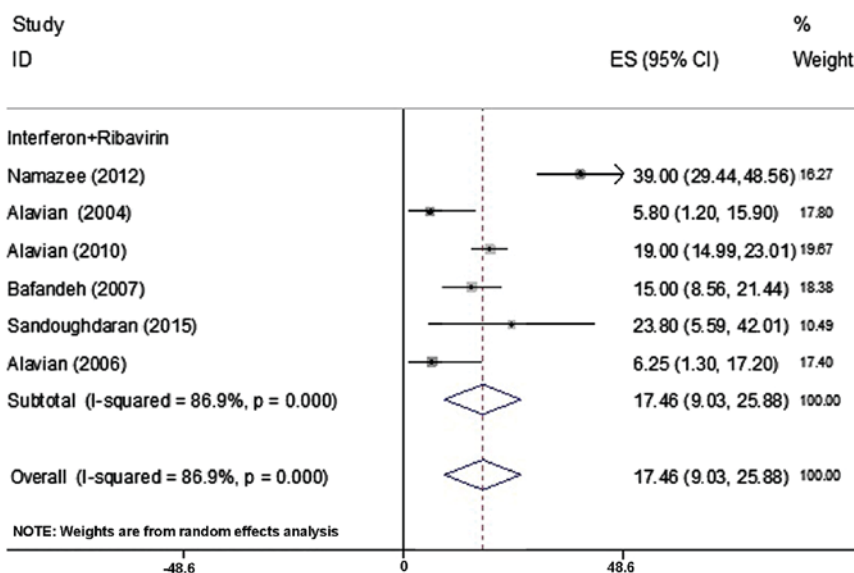


Figure 3. Forest plot of depression in primary studies. ES, effect size; CI, confidence interval.

between 5.8 and 39% (Table I). Combination of these 6 studies in the same manner as for fatigue, using the random effect

model revealed that the frequency of depression was 17.46% (95% CI; 9.03-25.88%; Fig. 3).

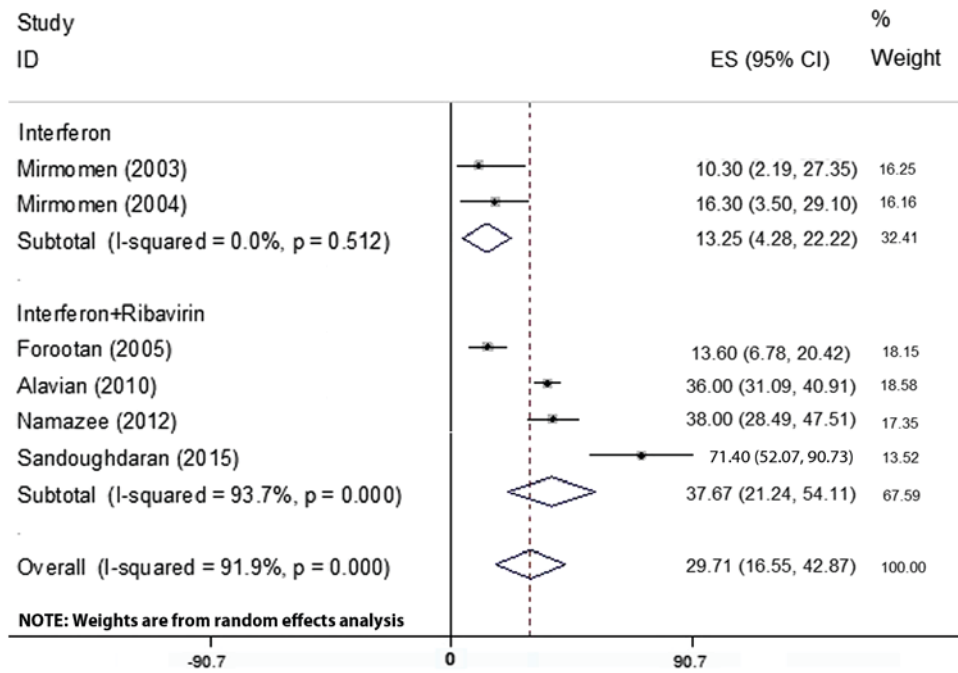


Figure 4. Forest plot of headache in primary studies. ES, effect size; CI, confidence interval.

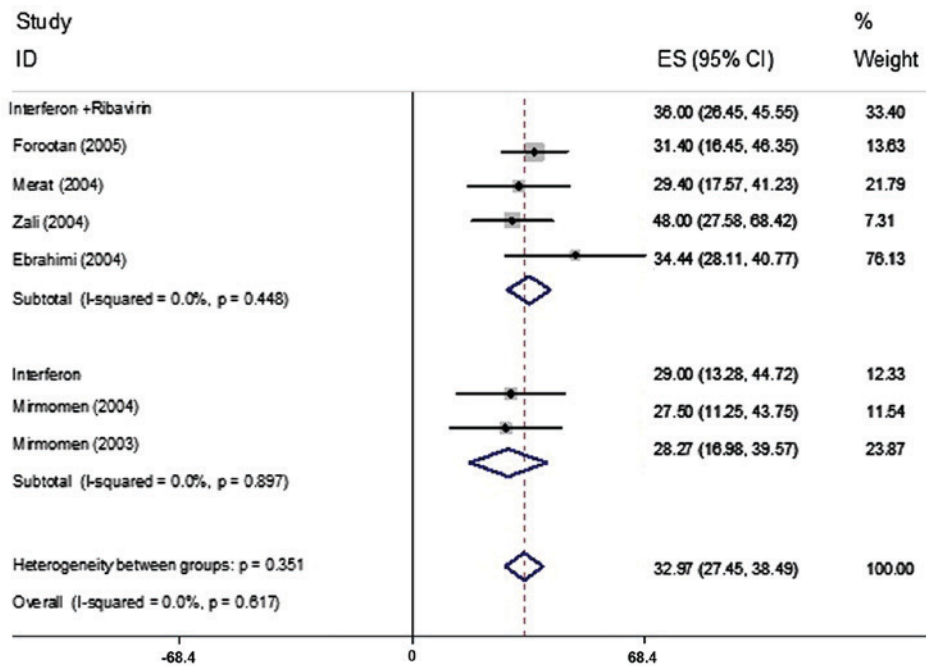


Figure 5. Forest plot of mood disorders in primary studies. ES, effect size; CI, confidence interval.

A total of 6 articles including 646 patients reported on the prevalence of headache, which ranged from 10.3-71.40% (Table I). Due to the heterogeneity in the results of the primary studies (Table II), the random-effects model used for assessment. By combining these 6 articles, it was revealed that headache had a prevalence of 29.71% (95% CI; 16.55-42.87%; Fig. 4).

The prevalence of mood disorders was reported in 6 articles comprising 275 patients and ranged from 27.5-48% respectively (Table I). Based on the heterogeneity between the results of the primary studies (Table II), the random-effects model was used for assessment. By combining of these 6

articles, mood disorders were determined to have a prevalence of 32.97% (95% CI; 27.45-38.49; Fig. 5).

The prevalence of insomnia was assessed in 7 articles including 897 patients and the rate of insomnia varied between 4.9 and 32.8% (Table I) (21,28). Based on the heterogeneity between the results of the primary studies (Table II), the random-effects model was used for assessment, revealing a frequency of insomnia in 16.28% (95% CI; 6.59-25.98%) of patients among the 7 studies (Fig. 6).

The prevalence of anorexia was assessed in 4 articles comprising 494 patients and was reported to range from 0-66.2%

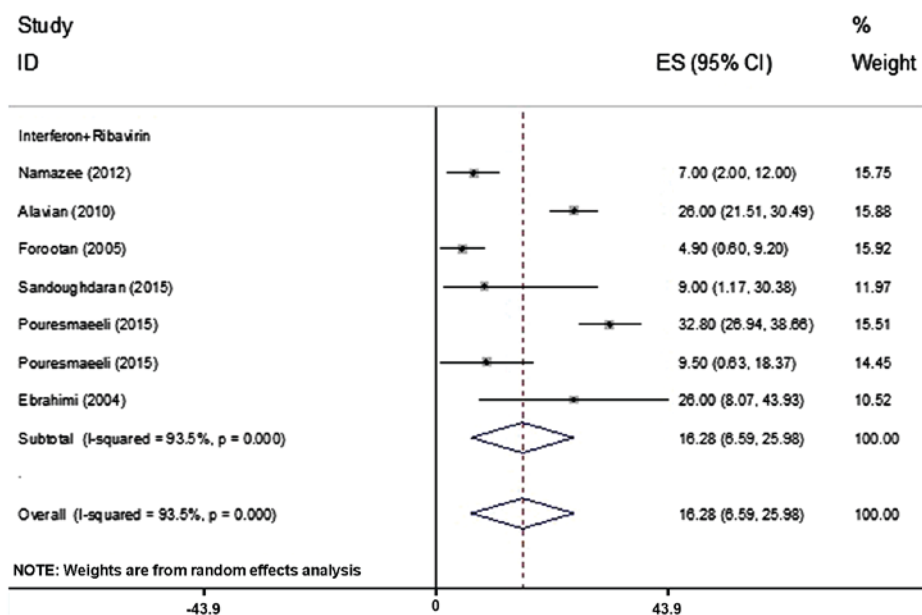


Figure 6. Forest plot of insomnia in primary studies. ES, effect size; CI, confidence interval.

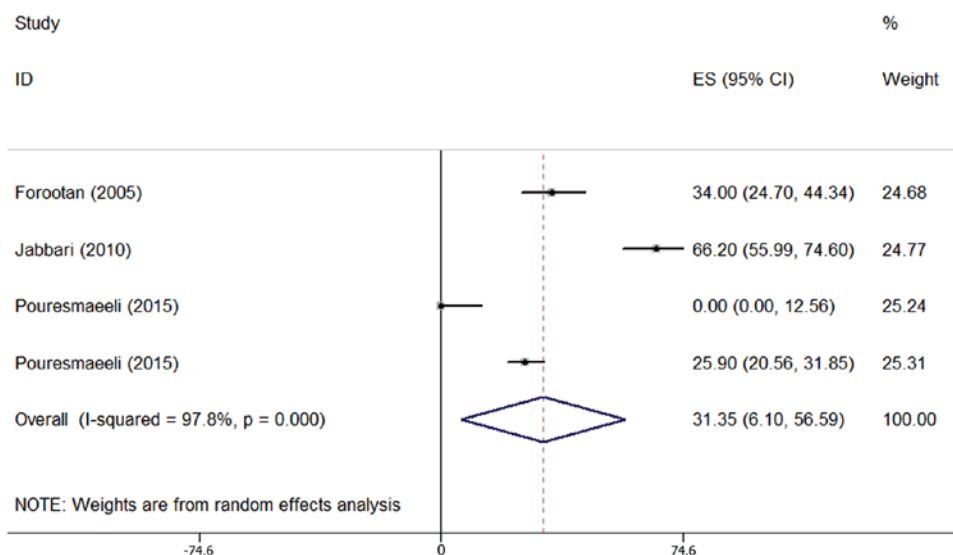


Figure 7. Forest plot of anorexia in primary studies. ES, effect size; CI, confidence interval.

(Table I). Due to the heterogeneity in the results of the primary studies (Table II), the random-effects model was employed. Combined analysis of these 4 articles revealed that anorexia occurred in 31.35% of patients (95% CI; 6.10-56.59%; Fig. 7).

In the present meta-analysis, adverse events of nervousness, dizziness, lethargy and irritability as well as morning headache were reported to be 34.7, 20, 21, 24 and 3.4%, respectively. Two studies reported on the prevalence of somnolence, which was 22.5 and 13.7%, respectively. Anxiety and excitability rates were reported as 41 and 16.1%, respectively. Weakness was reported in 3 studies with a prevalence of 0.5, 32.2 and 17.2%, respectively.

Egger's test was performed to assess the publication bias and the results are presented in Tables II. This test indicated that publication bias was not statistically significant (except for the outcome of anorexia). In addition, the age of the patients,

duration of drug use and publication year were considered as variables associated with heterogeneity in the Meta regression (Table III). The publication year had a significant role regarding the heterogeneity in the results for fatigue, depression and headache among the initial studies. Due to the small amount of data, subgroup analysis was not performed. Furthermore, due to the insufficient amount of evidence, it was not possible to consider the factors determining the heterogeneity regarding the outcome of anorexia.

The present study demonstrated that the majority of the psychiatric side effects, including weakness, anorexia, mood change, irritability, headache, fatigue, depression, nervousness, insomnia, anxiety, lethargy and dizziness were detected in patients who received ribavirin and interferon. Conversely, somnolence, morning headache and excitability were demonstrated in patients who ribavirin treatment. These results

Table III. Factors associated with heterogeneity between primary studies in the Meta regression analysis.

| Adverse event | Age | | Duration of drug use | | Publication year | |
|---------------|---------|---------|----------------------|---------|------------------|---------|
| | β | P-value | β | P-value | β | P-value |
| Fatigue | -0.7 | 0.735 | -0.7 | 0.598 | 8.9 | 0.058 |
| Depression | 0.06 | 0.963 | 0.2 | 0.690 | 2.9 | 0.033 |
| Headache | 0.8 | 0.661 | 0.8 | 0.032 | 3.9 | 0.002 |
| Insomnia | 0.2 | 0.832 | 0.1 | 0.639 | 0.2 | 0.875 |

suggest that taking ribavirin alone is the most effective for treatment of patients with HCV, particularly in individuals suffering from mental illness.

Discussion

The present meta-analysis study assessed the neuropsychiatric side effects among Iranian patients with hepatitis C that received peg IFN and ribavirin treatments for the first time, to the best of our knowledge. In all groups, the neuropsychiatric side effects with the highest and lowest frequency were fatigue 60.41% (95% CI; 39.18-81.64%) and insomnia 16.28% (95% CI; 6.59, 25.98%).

In the present study, fatigue was the most common neuropsychiatric symptom during IFN plus ribavirin or IFN therapy 60.41% (95% CI, 39.18-81.64%). It has been indicated that fatigue is associated with decreased adherence to treatment and reduced viral response (17,18,22). Certain patients receiving IFN plus ribavirin or IFN only develop fatigue without necessarily suffering from any somatic symptoms of depression or depressive emotional complaints, including sadness, hopelessness, guilt or anhedonia. Although patients receiving IFN-based therapy may have fatigue without fulfilling the criteria for clinical depression, fatigue may be considered to be an important symptom of depression (15,18,20-22).

For the above reasons, patients receiving IFN-ribavirin therapy who present with fatigue as well as sleep and/or appetite disturbance should be evaluated for clinical depression. In certain studies, headache is reported as one of the most frequent neuropsychiatric side effects of IFN-based treatment (occurrence rate, 29.6%) (20-25), which was similar to the results reported in the meta-analysis in the present study 29.61% (95% CI; 16.44-42.77%).

An important neuropsychiatric side effect, which is most frequently associated with IFN plus ribavirin or IFN monotherapy, is depression (16,17). In this context, depression occurs in a spectrum from minor to clinical depression in the range of 5.80% (95% CI, 1.20-15.90%) and 39% (95% CI, 29.44-48.56%). Certain studies have diagnosed depression based on certain symptoms (16,26,29), while others have defined depression as a syndrome characterized by a defined set of emotional and physical symptoms (15,17,20).

The prevalence of depression was determined to be 17.46% (95% CI, 9.03-25.88%) in the present meta-analysis. Although this is not a very high rate, it is important, as depression occurring during the treatment of hepatitis C may be associated with a reduced quality of life and also interfere with the patient pursuing to receive health care (20). Of note, as certain

adverse effects, including fatigue as well as sleep and appetite disturbances may overlap with depression, patients should be evaluated for major depression.

Numerous patients treated with IFN plus ribavirin or IFN only for hepatitis C experienced mood disorders. Of note, in the present meta-analysis the prevalence of mood disorders was determined to be 32.97% (95% CI, 27.45-38.49%). Irritability in patients receiving IFN plus ribavirin was reported by one study (17) and excitability was reported by one study on IFN (24). Certain patients have been suffered from sleep disturbances as a side effect of hepatitis treatment (26). In the present meta-analysis, the rate of insomnia was determined to be 16.28% (95% CI, 6.59-25.98%). Only two studies reported on the prevalence of somnolence, providing rates of 22.5 and 13.7% (24,25). Appetite disturbances were more frequent and anorexia was determined in 31.35% (95% CI, 6.10-56.59%) of patients according to the present meta-analysis. Nervousness (34%) (15), dizziness (20%) (17), lethargy (21%) (17) and anxiety (41%) (17) were reported in only one study for each. In the present meta-analysis, immune suppression and the length of treatment with peg IFN and ribavirin in chronic patients were not taken into account, which is a limitation of the present study.

In conclusion, the present meta-analysis indicated that treatment with IFN plus ribavirin or IFN only is associated with a wide range of neuropsychiatric side effects. Fatigue is the most common single neuropsychiatric symptom during IFN-based therapy. Other common neuropsychiatric side effects were mood disorders and depression, headache, anorexia and sleep disturbances. Certain patients who were treated with IFN plus ribavirin or IFN only experienced nervousness, dizziness, lethargy, irritability and anxiety. Finally, based on the results of the present meta-analysis, it is recommended that psychiatrists are increasingly involved in the care of such patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LD, TM and BM conceived and designed the study and wrote the manuscript. MRH and HJ performed the literature search and collected the data. MM performed the statistical analysis, and all authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing of interests.

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