

## WHEN DO PSYCHIATRIC SIDE EFFECTS EMERGE DURING ANTIVIRAL TREATMENT OF HEPATITIS C?

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### SUMMARY

**Background:** This retrospective study aimed to determine the time-frame regarding the first appearance of psychiatric side effects in the course of antiviral treatment and the subsequent referral to consultation-liaison psychiatric services.

**Subjects and methods:** Medical records of patients receiving combined antiviral treatment with alpha interferon and ribavirin for hepatitis C at a hepatology outpatient clinic and referred to psychiatric consultation between April 2000 and July 2011 were scrutinized.

**Results:** Time between the initiation of antiviral treatment and the first appearance of psychiatric symptoms was  $10.64 \pm 10.68$  weeks. Patients were referred to psychiatric examination  $16.1 \pm 12.7$  weeks after antiviral treatment had been commenced. The time frame of the emergence of psychiatric symptoms and the referral for psychiatric consultation did not correlate with the patients' age or sex. No relationship between substance/alcohol abuse and psychiatric history and the timing of psychiatric side effects and their assessment were found.

**Conclusions:** This study confirmed that psychiatric side effects appear late in the course of combined antiviral treatment arising after  $10.64 \pm 10.68$  weeks the treatment started. The results also showed that some patients' psychiatric symptoms appeared immediately after the beginning of the antiviral therapy. This finding underlines the importance of monitoring patients' psychiatric condition as soon as antiviral treatment commences.

**Key words:** hepatitis C - antiviral treatment - psychiatric side effects - substance/alcohol abuse - depression

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### INTRODUCTION

Several studies have examined psychiatric side effects of antiviral treatment with interferon-alpha and ribavirin in hepatitis C infected patients (Dieperink et al. 2000, Kovács et al. 2004, Pavlović et al. 2011). The most common psychiatric side effects are depressive and anxiety symptoms affecting 30-70% of patients depending on the methods employed (Quelhas & Lopes 2009). Some authors reported however serious side effects as psychosis (Quarantini et al. 2006) or suicidal behavior (Sockalingam et al. 2011) either. Besides fatigue, psychiatric side-effects are the most common causes of cessation of antiviral treatment (McHutchinson et al. 2002).

Psychiatric side effects can be prevented (Loftis & Hauser 2004) or effectively treated (Galvão-de Almeida et al. 2010) with adequate psycho-pharmacotherapy thereby maximizing the effects of antiviral treatment. Early detection of psychiatric symptoms, therefore, is of crucial importance (Gazdag & Szabó 2005). Raison et al. (2005) observed that psychiatric adverse effects appear at an increasing rate from the second month of antiviral treatment.

As our clinical experience was different, this retrospective study aimed to determine the time frame regarding the first appearance of psychiatric side effects in the course of antiviral treatment and the subsequent referral to consultation-liaison psychiatric services.

### SUBJECTS AND METHODS

This was a retrospective chart review. 'Szent Istvan' and 'Szent Laszlo' hospitals (SISLH) jointly run a hepatology outpatient clinic, the largest tertiary center for the treatment of hepatitis C in Budapest, Hungary supported by a consultation-liaison psychiatry service based in these hospitals. This consultation-liaison psychiatric service has been run by the same psychiatrist (GG) since 1999, thus the clinical examination and the documentation have been basically the same ever since.

Medical records of patients receiving combined antiviral treatment with alpha interferon and ribavirin for hepatitis C at the SISLH hepatology outpatient clinic and referred to psychiatric consultation between April 2000 and July 2011 were scrutinized.

The following information was extracted from the medical records: basic socio-demographic data, the starting

**Table 1.** Comparison of patients with respect to history of alcohol and substance abuse

	History of alcohol/ substance use (n=14)	No history of alcohol/ substance abuse (n=111)	Statistics
Age (years)	36.1±5.8	47.8±11.0	p<0.001
Time lag between the start of antiviral therapy and first psychiatric symptoms (weeks)	6.4±7.8	11.0±10.9	n.s.
Time lag between the start of antiviral therapy and psychiatric evaluation (weeks)	13.2±10.3	16.4±12.6	n.s.

n.s. = not significant

**Table 2.** Comparison of patients with respect to history of psychiatric disorders

	History of psychiatric disorders (n=47)	No history of psychiatric disorders (n=78)	Statistics
Age	47.8±9.8	45.5±11.9	n.s.
Time lag between the start of antiviral therapy and first psychiatric symptoms (weeks)	11.7±11.4	10.1±10.3	n.s.
Time lag between the start of antiviral therapy and psychiatric evaluation (weeks)	17.2±11.8	15.5±13.3	n.s.

date of antiviral treatment and that of the first psychiatric consultation, the first appearance of psychiatric symptoms, alcohol and drug use psychiatric history, current psycho-pharmacotherapy and the psychiatric diagnoses established at the first consultation.

During the study period, 125 patients on antiviral therapy were referred for psychiatric evaluation; 4 patients were referred twice. Three patients were excluded from the study: one for co-morbid substance abuse resulting in drug-induced psychosis, one had only mild symptoms not fulfilling any diagnostic criteria and the third one refused to be interviewed. The mean age of the study sample was 46.36±11.19 years; 68 were female. Male patients were significantly younger than females (42.3±11.5 vs. 49.6±9.8; p<0.001).

### Statistical analyses

The data were analyzed with the SPSS Version 12.0 statistical software. T-test and chi-square test were used for continuous and discrete variables, respectively. Pearson's correlation coefficient was employed to determine the correlations between history of psychiatric contact and that of alcohol/substance abuse and the occurrence of psychiatric side effects.

## RESULTS

The time between the initiation of antiviral treatment and the first appearance of psychiatric symptoms was 10.64±10.68 weeks (range: 1-48 weeks); this could be determined with certainty for 85 (67.5%) patients. Patients were referred to psychiatric examination 16.1±12.7 weeks (range: 1-68 weeks) after antiviral treatment had been commenced. The time frame of the emergence of psychiatric symptoms and the referral for psychiatric consultation did not correlate with the patients' age or sex. Eleven patients had a history of intravenous drug abuse and 4 periodically abused

alcohol. The relationship between substance/alcohol abuse and psychiatric history and the timing of psychiatric side effects and their assessment are shown in Tables 1 and 2.

The three most common psychiatric diagnoses according to ICD-10 categories were mixed anxiety and depressive disorder (41.8%), moderate depressive episode (24.0%), and other specified anxiety disorders (8.8%). Forty-seven patients (37.6%) had psychiatric contact before starting antiviral treatment; 11 patients (8.8%) were on psychotropic drugs, 9 and 4 received benzodiazepines and antidepressants, respectively.

## DISCUSSION

The study confirmed that psychiatric side-effects appear late in the course of combined antiviral treatment (Capuron et al. 2002) arising after 10.64±10.68 weeks the treatment started. The results also showed that some patients' psychiatric symptoms appeared immediately after the beginning of the antiviral therapy. This finding underlines the importance of monitoring patients' psychiatric condition as soon as antiviral treatment commences. Close monitoring and regular screening for the psychiatric symptoms could reduce the delay of the introduction of their adequate treatment (Gazdag & Szabó 2005). In this study nearly 6 weeks elapsed from the appearance of the first psychiatric symptom until psychiatric referral. In accord with the literature (Raison et al. 2005), mainly depressive and anxiety symptoms dominated the adverse psychiatric effects in this study.

In patients with alcohol and substance abuse history, psychiatric symptoms occurred nearly 5 weeks earlier once antiviral therapy had been started, but this difference was not statistically significant (p=0.20). Clinical wisdom holds that for patients with history of substance abuse psychiatric symptoms usually appear in the second month of the antiviral treatment, while those with no previous abuse this commonly happens only at

the end of the third month. This observation is rather preliminary as only 14 patients with substance abuse history were in this study and they were significantly younger than those with no previous drug abuse.

In this study, previous psychiatric contact did not impact on the time-frame of psychiatric side-effects and subsequent psychiatric referral. Yet, from a clinical point of view, history of psychiatric disorders has major implications: it is plausible to assume that having previous psychiatric contact is itself a selection criterion for referral. Another conceivable explanation might be that patients with psychiatric history are more vulnerable for psychiatric side effects of the antiviral treatment, although the heightened vulnerability was not expressed in earlier appearance of the symptoms.

In contrast to the relatively high rate of psychiatric contacts in this sample (37%), only 8.8% of patients were on ongoing psychiatric pharmacotherapy. It is all the more surprising considering that hepatitis C itself is associated with a higher rate of depression (24-32%) (Dieperink et al. 2000), and approximately two-thirds of depressed patients need antidepressant treatment (Lee et al. 1997).

The most important limitations of this study are due to its retrospective nature. Only patients referred to consultation were included in the study, but it is likely that psychiatric symptoms had been present and could not be identified in an unknown number of patients. It is also possible that some patients had been seeking help at other psychiatric services. As hepatitis C infection itself is also associated with higher psychiatric comorbidity, lack of a control group constitutes a further limitation of the study.

## CONCLUSIONS

Although psychiatric side effects in some patients appear as early as the first week of antiviral treatment of hepatitis C, their mean occurrence falls on the third month. Psychiatric consultations usually take place only after the fourth month. As early detection and effective treatment of psychiatric side effects are essential to optimize antiviral treatment, the gap between the appearance of the psychiatric symptoms and the psychiatric consultation should be as short as possible. This goal could be reached with periodical screening and close monitoring of patients' psychiatric condition during antiviral treatment.

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**Conflict of interest :** None to declare.

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