

## PSYCHIATRIC ADVERSE EFFECTS OF INTERFERON THERAPY

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### **Abstract**

*A number of data support the involvement of immunological mechanisms in the etiology of psychiatric disorders. The nervous and immune systems are physiologically integrated and influence each other's functioning.*

*Clinical studies have reported a larger number of psychiatric symptoms consecutive to immunomodulating interferon therapy. The most frequent are depression, suicidal behavior, manic syndrome, anxiety disorders, psychotic disorders and delirium associated with an array of unspecific psychiatric symptoms: fatigue, irritability, psycho-motor retardation, decreased libido, insomnia, concentration difficulties and attention deficit. Another undesired consequence of interferon therapy is the worsening of a preexistent psychiatric disorder. Thus, a history of psychiatric disorder is currently one of the contraindications of interferon therapy.*

*Psychiatric adverse events may occur either shortly after the initiation of therapy, or as a result of ongoing treatment, but most adverse events occur after 3 weeks of treatment.*

*Although there are relatively few studies on statistically significant patient samples, current data underline the importance of managing these effects and also the most indicated treatment strategies. Therefore, an improved psychiatric management of these adverse effects may change the gastroenterologist's decision to exclude from treatment high – risk patient categories such as those with mood disorders, alcohol or drug abuse, or other addiction.*

**Keywords:** interferon, depression, neurotoxicity

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### **Introduction**

There is extensive evidence of the involvement of immune mechanisms in psychiatric disorders. It is currently known that the nervous system and the immune system are physiologically integrated, influencing each other's functioning. Thus, the potential involvement of an autoimmune mechanism in schizophrenia was mentioned as early as 1912. The relationship between psychiatric disorders and immunological changes is currently studied and confirmed in schizophrenia and major depressive episode. Moreover, there are many other disorders in which the immune system appears to have a role, such as dementia, especially Alzheimer's, autism, antisocial behavior and Parkinson's disease [1].

Starting from this body of data, it is expected that a plethora of psychiatric symptoms would be ascertained during interferon therapy. Among these, depressive symptoms, suicidal behavior, manic syndrome, anxiety disorders, adjustment disorders, psychotic disorders and delirium – acute confusion were reported. A series of non –

specific symptoms such as fatigue, irritability, psycho – motor lassitude, decreased libido, concentration difficulties, attention deficit and insomnia were also noted [2]. Interferon therapy was also shown to generate personality changes with irritability, anxiety, impulse control disorders [3]. Moreover, interferon was shown to cause worsening of a pre-existing mental disorder [4].

Interferon neurotoxicity appears to be dose-dependent. An important role is played by the daily dose, means of administration, combination with other medications [5]. A history of mental disorder is an important predictive factor for occurrence of psychiatric symptoms after interferon therapy [6]. Psychiatric adverse events may occur either shortly after the start of therapy, or later as a result of continuing treatment. Although most adverse events occur after 3 weeks of treatment, non-specific symptoms may occur very early. The incidence of late-onset adverse events is estimated by various studies among 0 and 70%. Although there are relatively few studies on statistically significant patient samples, current data emphasize the importance of managing these effects and also the most indicated treatment strategies [7].

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### Depression Secondary to Interferon Therapy

It is by far the most frequent complication. Research estimates an incidence of depression during interferon therapy between 5 and 15% [8]. Significant depressive symptoms that do not meet the criteria for major depressive episode were reported more frequently: between 21 and 58% [7]. Although depressive symptoms may occur in the first week of treatment, the peak of incidence of depression is recorded between the 1st and the 3rd month of treatment. The intensity of depression during interferon therapy varies from mild reactive depression to major depressive episode.

A number of risk factors for depression secondary to interferon therapy were identified: mood and/or anxiety symptoms prior to therapy, female gender, increased doses of interferon with extensive duration of treatment [2].

Two clinical types of depression were described, with an importance for treatment approach. On the one hand, a specific depressive syndrome with altered mood, anxiety and cognitive deficit was shown to effectively respond to selective serotonin reuptake inhibitors (SSRIs), e.g. paroxetine, sertraline or citalopram. On the other hand, a neurovegetative syndrome with fatigue, anorexia, pain complaints and lassitude favorably responds to dual antidepressants, e.g. venlafaxine, mirtazapine, milnacipram [9].

Some authors recommend antidepressant medication prior to interferon therapy [10], especially in persons with risk factors for depression [11]. Prophylactic treatment with paroxetine (20 mg/day) was well tolerated and decreased both the incidence and the severity of interferon induced depression [12]. Prophylactic treatment with citalopram (20 mg/day) was well tolerated, preventing the onset of severe depression [13].

Recent studies prove the efficacy of antidepressant medication in depression secondary to interferon therapy, allowing most patients to complete interferon treatment. Thus, 78.6% of patients with interferon-induced depression were able to continue IFN- $\alpha$  treatment as initially scheduled [14].

### Suicide and suicidal behaviors

It is the most severe complication, directly influencing *quo ad vitam* prognosis. Fortunately, suicidal behavior accounts for a minority of psychiatric adverse effects of interferon. Suicidal behavior is not an adverse event *per se*, but a consequence of other adverse reactions – most often occurring within a major depressive episode [15]. Less frequently, it may be generated by delirium episodes or by a non – specific adverse event: impairment of impulse control [4].

Careful monitoring of persons with depressive symptoms during interferon therapy is the most effective strategy to identify and subsequently prevent suicide risk.

### Manic Syndrome

It is a rarely encountered situation, estimated to less

than 1% of cases [6]. It has the same incidence in patients with no personal or family history of psychiatric disorders, hence the proposed denomination of “tertiary mania”. The manic episode almost always occurs in the final stages of interferon therapy.

The manic episode may rarely appear subsequently to antidepressant medication (in which case stopping the antidepressant medication may be sufficient and interrupting the interferon therapy may not always be required), in antidepressant treatment both prophylactic, and in patients presenting with interferon-induced depression.

The manic syndrome in this case exhibits clinical features such as increased irritability and agitation, while the euphoria specific to manic syndrome is much more rare.

It is a psychiatric emergency that requires hospitalization and specific therapeutic approach. There is a consensus that interruption of interferon therapy is compulsory if the manic episode is not the consequence of antidepressant medication.

### Anxiety Disorders

They are less mentioned in studies. The reported incidence of anxiety disorders induced by interferon ranges between 1.4 and 3.3% [16]. In some cases, these disorders are regarded as preexistent to interferon therapy, while in others anxiety is a clinical feature of the depressive episode. Interferon therapy leads to the reactivation or worsening of preexistent anxiety disorders [17].

Recommended anxiolytic medication, if necessary, includes short-acting benzodiazepines such as: alprazolam, lorazepam, bromazepam or oxazepam.

### Adjustment Disorders

They are commonly generated by communicating the hepatitis C diagnosis and its severity to the patient. In less frequent cases, the psychological trauma refers to indicating interferon therapy and explaining its toxicity and risks [4].

The most common management strategy is counseling. A pharmacological approach of symptoms is rarely indicated. Treatment is adjusted to the dominating symptoms (e.g. anxiety, insomnia or depressive mood).

### Psychotic Disorders

Their incidence is very low – it was reported in less than 1% of patients treated with interferon [6]. Psychotic symptoms occur between the first and third month of treatment.

Clinical features include hallucinations and/or paranoid delusions. Symptoms commonly remit when interferon therapy is interrupted, in few cases specific antipsychotic medication is required [8].

### Delirium – acute confusion state

Its incidence is low. It always occurs shortly after the initiation of interferon therapy [3].

It is characterized through disorientation, lethargy, somnolence, psycho – motor retardation, speech difficulties,

parkinsonism. Psychotic symptoms, especially hallucinations, often overlap on this background [18].

Treatment strategy includes discontinuation of interferon therapy and treatment with first-generation antipsychotics, especially haloperidol. More recent studies recommend second-generation antipsychotics, especially risperidone.

### Non – Specific Psychiatric Symptoms

Incidence of clinically significant irritability was reported as 3% [16]. The therapeutic strategy recommended by most authors is tioridazin. Avoiding anti-epileptic mood stabilizers (carbamazepine, valproic acid) is recommended, because of their hepatotoxic effect.

As an isolated symptom, insomnia has an incidence of up to 10%. Correcting insomnia may be achieved with: sleep-inducing benzodiazepines (nitrazepam, flunitrazepam), or non-benzodiazepine sleep aids (zopiclone, zolpidem) [16].

### Cognitive Decline

Cognitive decline was ascertained throughout interferon therapy [19]. Decrease in cognitive skills may be documented as decreased performance in cognitive testing, more specifically a decrease of 2 to 5 points in Mini Mental State Examination (MMSE) scores. Cognitive decline was shown not to be exclusively generated by depression or other psychiatric adverse effects of interferon [20]. Cognitive decline is accompanied by specific changes in EEG tracings [21].

Decrease in cognitive performance and identified changes of EEG tracings occur relatively early and can be ascertained after 2 weeks of interferon therapy. They slowly but gradually increase in intensity and are reversible after the end of interferon therapy.

### Conclusions

A deeper understanding of the mechanisms underlying the psychiatric adverse effects induced by IFN- $\alpha$  is crucial for extending the availability of this treatment for patient groups that have been excluded in current protocols.

An improved psychiatric management of these psychiatric adverse effects may allow the gastroenterologist not to exclude from treatment patient groups deemed as high-risk, such as those with mood disorders, alcohol or drug abuse, or addiction.

### References

1. Berthold-Losleben M, Heitmann S, Himmerich H. Anti-inflammatory drugs in psychiatry. *Inflamm Allergy Drug Targets*, 2009; 8(4):266-276.
2. Schaefer M, Capuron L, Friebe A, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol*, 2012; 57(6):1379-1390.
3. Schaefer M, Engelbrecht MA, Gut O, Fiebich BL, Bauer J,

Schmidt F, et al. Interferon alpha (IFN $\alpha$ ) and psychiatric syndromes: a review. *Prog Neuropsychopharmacol Biol Psychiatry*, 2002; 26(4):731-746.

4. Trask PC, Esper P, Riba M, Redman B. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *J Clin Oncol*, 2000; 18(11):2316-2326.

5. Fontana RJ. Neuropsychiatric toxicity of antiviral treatment in chronic hepatitis C. *Dig Dis*, 2000; 18(3):107-116.

6. Hosoda S, Takimura H, Shibayama M, Kanamura H, Ikeda K, Kumada H. Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. *Psychiatry Clin Neurosci*, 2000; 54(5):565-572.

7. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs*, 2005; 19(2):105-123.

8. Debien C, De Chouly De Lenclave MB, Foutrein P, Bailly D. Alpha-interferon and mental disorders. *Encephale*, 2001; 27(4):308-317.

9. Loftis JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *J Affect Disord*, 2004; 82(2):175-190.

10. Hou XJ, Xu JH, Wang J, Yu YY. Can Antidepressants Prevent Pegylated Interferon- $\alpha$ /Ribavirin-Associated Depression in Patients with Chronic Hepatitis C: Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials? *PLoS One*, 2013; 8(10):e76799.

11. Kraus MR, Schäfer A, Al-Taie O, Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. *J Viral Hepat*, 2005; 12(1):96-100.

12. Raison CL, Woolwine BJ, Demetrashvili MF, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Aliment Pharmacol Ther*, 2007; 25(10):1163-1174.

13. Schaefer M, Schwaiger M, Garkisch AS, Pich M, Hinzpeter A, Uebelhack R, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol*, 2005; 42(6):793-798.

14. Kraus MR, Schäfer A, Faller H, Csef H, Scheurlen M. Paroxetine for the treatment of interferon-alpha-induced depression in chronic hepatitis C. *Aliment Pharmacol Ther*, 2002; 16(6):1091-1099.

15. Reith DM, Edmonds L. Assessing the role of drugs in suicidal ideation and suicidality. *CNS Drugs*, 2007; 21(6):463-472.

16. Maddock C, Baita A, Orrù MG, et al. Psychopharmacological treatment of depression, anxiety, irritability and insomnia in patients receiving interferon-alpha: a prospective case series and a discussion of biological mechanisms. *J Psychopharmacol*, 2004; 18(1):41-46.

17. Hurlock EC 4th. Interferons: potential roles in affect. *Med Hypotheses*, 2001; 56(5):558-566.

18. Giunta B, Somboonwit C, Nikolic WV, Rrapo E, Tan J, Shapshak P, Fernandez F. Psychiatric implications of hepatitis-C infection. *Crit Rev Neurobiol*. 2007; 19(2-3):79-118.

19. Lieb K, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, Janssen G, et al. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFN $\alpha$ ): results from a prospective study. *Eur Psychiatry*, 2006; 21(3):204-210.

20. Myint AM, Schwarz MJ, Steinbusch HW, Leonard BE. Neuropsychiatric disorders related to interferon and interleukins treatment. *Metab Brain Dis*, 2009; 24(1):55-68.

21. Kamei S, Sakai T, Matsuura M, et al. Alterations of quantitative EEG and mini-mental state examination in interferon-alpha-treated hepatitis C. *Eur Neurol*, 2002; 48(2):102-107.