

Recommendations

Evaluation and management of psychiatric disorders in adult patients infected by hepatitis C virus and treated with (peg) interferon alfa and ribavirin

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KEY POINTS

Close cooperation between the various healthcare professionals involved in the follow-up of any patient infected by HCV (hepatologists, infectious diseases specialists, psychiatrists, general practitioners, addictologists etc.) is essential even before starting anti-hepatitis C treatment and must continue throughout the treatment and in the months following treatment discontinuation.

Before starting anti-hepatitis C treatment

- ▶ The initiation of **anti-hepatitis C treatment is not usually an emergency**. It is important to take enough time to obtain a psychiatric assessment of the patient and to identify situations for which specialized advices are necessary:
 - ▶ **The opinion of a psychiatrist should be sought in the following cases:**
 - a history of psychiatric disorder having requiring patient hospitalization or specialized consultation
 - treatment by mood stabilizers or antipsychotics in the past year
 - a history of any psychiatric disorder during former treatment by interferon alfa
 - a current major depressive episode, suicidal risk, bipolar disorder and/or a current behavioural problem.
 - ▶ **The opinion of the addictologist should be sought** for patients currently using drugs or having used them in the past year.
 - ▶ **The psychiatric state of the patient must be stabilized before starting anti-hepatitis C treatment.**
 - ▶ **The patient and his close relatives must be informed of the risks related to the treatment.**

During anti-hepatitis C treatment

- ▶ **A psychiatrist should be contacted quickly in the event of:**
 - suicidal ideation
 - aggressiveness directed against others or significant behaviour disorders
 - presence of signs of (hypo)mania (euphoria, excessive agitation)
 - persistence and/or worsening of depressive symptoms
 - request from the patient to consult
 - and more generally in case of doubt
- ▶ **The opinion of the addictologist should be sought** in the event of an increase in drug-taking and/or destabilization of the opiate substitution treatment, or even an increase in need for anxiolytics.

- ▶ **In the event of severe psychiatric adverse effects, the continuation of the anti-hepatitis C treatment must be reassessed jointly by the hepatologist and the psychiatrist.** A reduction in the dosage regimen of interferon alfa is not recommended.
- ▶ **The occurrence of behavioural problems** (irritability, impulsiveness, aggressiveness, hyperemotivity) **should encourage the doctor to look for other associated psychiatric disorders, particularly episodes of mania or hypomania and/or concomitant drug use** which could justify a specialist opinion.
- ▶ In the treatment of moderate to severe depressive episodes, it is preferable to use a **selective serotonin re-uptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI)** as a first-line drug. For the treatment of (hypo)manic episodes, **lithium salts are to be preferred.**

Following anti-hepatitis C treatment

- ▶ Psychiatric symptoms have been reported several months after discontinuation of anti-hepatitis C treatment. Because of this, the **monitoring of the patient's psychiatric state should be continued after anti-hepatitis C treatment discontinuation.** The patient, his attending doctor and his close relatives should be informed of the possibility of the occurrence or aggravation of psychiatric symptoms even after the discontinuation of anti-hepatitis C treatment and the need for rapid consultation if such symptoms are observed.

INTRODUCTION

In mainland France, the prevalence of hepatitis C (HCV) anti-virus antibodies is estimated at 0.84% of the general population aged from 18 to 80 years old. It should be noted that in prison, the prevalence of hepatitis C is estimated at four to five times higher than that for the public at large. It is considered at 6 to 7% in psychiatric patients and at nearly 60% in drug users. The reference treatment for chronic infection by HCV consists of a weekly injection of pegylated interferon alfa associated with a daily dose of ribavirin for 6 months to 1 year according to the viral genotype. This treatment is associated with adverse psychiatric effects which are currently the major concern in patient management for this condition. Indeed, they are regarded as an obstacle to starting treatment and a cause of poor compliance and stopping treatment, thus compromising the chances of eradicating the virus.

Adverse psychiatric effects are very frequently reported during anti-hepatitis C treatment and are characterized generally by depressive symptoms, anxiety, mood and behaviour disorders (aggressiveness, impulsiveness, irritability and hypermotivity). There is a suicidal risk (attempted suicides and/or completed suicide). Manic episodes and acute psychotic states have also been reported. The mechanism at the origin of these adverse effects has not been elucidated. In addition, depressive signs or mood disorders can be inherent in the HCV infection itself.

Because of diversity of the observed signs, early and adapted evaluation and management of these adverse effects would seem to be an essential element of the global management of the patient in order to guarantee an optimal virological response in the treatment of HCV infection.

This document, developed by a multi-field group of specialists, aims at proposing recommendations for health professionals in order to improve the evaluation and the management of the psychiatric disorders in HCV-infected patients treated with (peg) interferon alfa and ribavirin.

The best patient management requires close cooperation between the various actors involved in patient follow-up (hepatologist, infectious diseases specialist, psychiatrist, attending doctor, addictologist etc.).

Medical coordination around the patient must be set up even before starting anti-hepatitis C treatment and must be continued throughout the treatment and in the months following the discontinuation of treatment.

It is recommended that the attending doctor is associated with the care management of the patient. Indeed, he is the patient's and the patient's relatives' first line of communication and can liaise with the other healthcare professionals implied in the follow-up of the patient.

I - Before initiating hepatitis C treatment

Initiating treatment by interferon alfa and ribavirin in a patient infected by chronic hepatitis C virus is not usually an emergency.

In this context, the necessary time should be taken in order to assess the current psychiatric state of the patient and possible risk factors, making it possible to identify the patients for whom a specialized opinion will be required before beginning the treatment.

As much as possible, the doctor should encourage the **presence of the spouse or a close relation during discussions with the patient**, as it is often easier for a relation or friend to testify to mood and behaviour disorders which it might be difficult for the patient himself to express or which he may minimize. This trusted person is made aware, just like the patient, of the risk of occurrence of symptoms as soon as the treatment is begun and will be able to inform the doctor about them if necessary.

a) Inquiring about previous psychiatric problems

First of all, the patient should be interviewed concerning previous psychiatric problems (particularly major depression episode, suicide attempts or bipolar disorders). The patient's general practitioner is the most important source of information in this regard. If the doctor has observed:

- a psychiatric disorder having required patient hospitalization or a specialized consultation
- a treatment by mood stabilizers or antipsychotics in the past year
- or psychiatric symptoms during a former treatment by interferon alfa,

he should ask the opinion of a psychiatrist before beginning anti-hepatitis C treatment.

- In the event of drug abuse or dependency in the previous year, the opinion of an addictologist should be sought before beginning the treatment.

Use of syringes for the administration of interferon alfa may be problematic for intravenous drug users. So before beginning anti-hepatitis C treatment in these patients, the subject should be brought up with them and the addictologist.

The attending doctor is particularly involved in this and is usually the easiest professional to contact. The ancillary medical teams are also important in behavioural and social therapeutic care management.

b) Assessment of the current psychiatric state of the patient

Secondly, an evaluation of the current psychiatric state of the patient should be carried out to look for:

- a major depressive episode
- a suicidal risk
- a bipolar disorder (alternation of phases of exaltation and depression)
- a behavioural problem (aggressiveness, impulsiveness, irritability and hyperactivity)
- a current drug use

This first stage of assessment can be carried out by the doctor who initiates the anti-hepatitis treatment. After the consultation he will be in a position to refer the patient or not for a specialized consultation with a psychiatrist or an addictologist before beginning the anti-hepatitis C treatment.

Although to date there is no standardized and validated tool specifically developed for the diagnosis of psychiatric disorders in the context of hepatitis C, proper use of the MINI (Mini International Neuropsychiatric Interview) is considered as being appropriate in this sense, as it can help the doctor in his evaluation of the current psychiatric state of the patient and to guide him in his decision to refer the patient for a psychiatric opinion.

Three modules of the MINI whose aims are to identify a major depressive episode, a manic or hypomanic episode and to evaluate the suicidality are set out in appendix of the present document in order to help the doctor track psychiatric disorders. The levels of suicide risk (mild, moderate and severe) are only given as an indication and should not lead to an underestimation of the suicide risk. Moreover, a psychiatric opinion should be sought if a suicidal risk is identified whatever the level of risk (including low).

The group of specialists considers that the number of patients that have to be definitively excluded from treatment by (peg) interferon alfa and ribavirin for psychiatric reasons is very small. On the other hand, it is essential to ensure that the psychiatric state of the patient is stabilized before beginning anti-hepatitis C treatment.

c) Drug treatment management for patients at risk of psychiatric disorders before beginning anti-hepatitis C treatment

The patients at risk are those for whom current or previous psychiatric disorders have been identified.

For these patients, the need for antidepressant or antipsychotic treatment before beginning the anti-hepatitis C treatment must be evaluated on a case-by-case basis by the psychiatrist.

As a reminder, antidepressants can induce manic changes of mood, particularly in bipolar patients. The management of these patients must therefore be the subject of a specialized opinion.

d) Preventive treatment of depression in patients without identifiable risk factors

There are few studies available evaluating the preventive use of antidepressants in the context of hepatitis C. Their methodology is open to criticism and they only include a limited number of patients. To date they do not allow to evaluate the benefit/risk ratio of the preventive use of antidepressants in patients who are to receive anti-hepatitis C treatment.

e) The importance of informing the patient and his close relatives about the risks related to treatment:

Before beginning anti-hepatitis C treatment, the patient and if possible his close relatives should be informed of the risks related to the treatment. The presence of the spouse or a close relation during the initial consultation, and more generally during follow-up consultations, is therefore recommended. The information for the patient and his close relatives must relate to:

- the adverse effects linked to anti-hepatitis C treatment.
- the risk of mood changes, depression, irritability, auto- or hetero-aggressiveness, impulsiveness, hyperactivity, sleep disorders, tiredness etc.
- the importance of warning a health professional as soon as any of these symptoms occur.

II - During anti-hepatitis C treatment

a) Patient follow-up and detection of psychiatric disorders during the treatment

Faced with the frequency and diversity of the psychiatric adverse effects associated with anti-hepatitis C treatment and because of their potential severity, increased vigilance should be observed in order to detect and deal with any change in the usual state of the patient in the most appropriate manner and as soon as possible.

Depressive symptoms and sleep disorders are the problems most frequently observed. Sleep disorder can also be one of the symptoms of depression and anxiety as well as manic or hypomanic episodes. The symptoms of these various disorders must therefore be systematically looked for in a patient presenting sleep disorders. Isolated insomnia can benefit from symptomatic treatment over a short period from but if it persists the doctor should consider the existence of other problems and change to a more specific therapeutic strategy.

Moreover, anxiety, mood disorders, behavioural problems (irritability, aggressiveness, impulsiveness and hyperactivity) as well as manic episodes and psychotic states have also been observed. Suicidal thoughts, cases of attempted suicide and completed suicide have also been reported.

The adverse effects of a psychiatric nature typically occur between the first and the third month of the anti-hepatitis C treatment but can also appear throughout the treatment and several months after discontinuation of the treatment; for this reason, the psychiatric state of the patient should be supervised regularly throughout the whole anti-hepatitis C treatment. More frequent consultations, if possible every two weeks, are recommended during the first months of treatment and the attending doctor can be called upon for this. Patients already treated with antidepressants, mood stabilizers, antipsychotics or anxiolytics should especially be monitored. Multi-disciplinary patient management is recommended for these patients.

At each consultation, the doctor in charge of the therapeutic follow-up of the HCV infection should have a discussion with the patient. MINI modules (cf. appendix of this document – the same questionnaire as that for psychiatric assessment at the beginning of the treatment) can be used to help with screening, the objective being the early detection of any change in the psychiatric state of the patient (particularly the presence of depressive episodes, (hypo)manic episodes and evaluation of the risk of suicidality).

Any evocative sign should lead the doctor to decide upon a suitable therapeutic strategy.

TSH dosing in the event of asthenia or of depression, apart from the usual testing every two or three months, should be carried out in order to exclude hypothyroidism which may be secondary to the treatment by interferon alfa.

A psychiatrist should be contacted quickly in the event of:

- suicidal ideation
- aggressiveness directed against others disturbing family or social life or significant behaviour disorders
- presence of (hypo)manic signs (euphoria and/or excessive agitation)
- persistence and/or worsening of depressive symptoms
- request from the patient to consult
- and generally in case of doubt

The continuation of the anti-hepatitis C treatment must be re-evaluated jointly by the hepatologist and the psychiatrist.

A reduction in the doses of interferon alfa in this context has not been evaluated. It is unlikely that this would have an impact on psychiatric disorders. Moreover, there is a risk of the anti-hepatitis C treatment not being effective. Consequently, the group does not recommend a reduction in the dosage of interferon alfa.

Concerning drug addicts, an addictologist should be called upon in the event of changes in the normal behaviour of the patient such as an increase in drug-taking and/or destabilization of the opiate substitution treatment or even an increase in need for anxiolytics.

b) Management of psychiatric disorders occurring during treatment

1. Non-pharmacological patient management

Psychotherapy or individual psychological or group therapy may be provided for the patient.

Moreover, medico-social management is recommended in the event of psychiatric symptoms which are affecting the social, family and/or professional life of the patient.

For drug addicts, the medical coordination and cooperation with the patient must be reinforced. This includes exchanging information; genuine coordination between the doctors involved (hepatologist and addictologist) as well as their teams and reinforced psychosocial support.

2. Pharmacological patient management, psychotropic drug selection criteria

- **Depressive episodes:** (see also the recommendations on the good use of antidepressants in the treatment of depressive disorders and anxiety disorders in adults (October 2006) http://afssaps.sante.fr/pdf/5/rbp/reco_antide_presseur_adultes.pdf)

→ Treatment of mild depressive episodes

Major depressive episodes of mild intensity do not systematically require treatment by antidepressants. Advice about living healthily (such as stopping alcohol and doing exercise or taking up a relaxation technique) and psychotherapy can be given to the patient.

→ Treatment of moderate to severe depressive episodes

The seriousness of the episodes is evaluated according to their number, intensity and repercussions of the depressive symptoms.

Choice of antidepressant

Because of their effectiveness and their well established tolerance profiles, it is preferable to use a selective serotonin reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI).

However studies evaluating the use of these antidepressants in subjects with depression taking interferon alfa are rare and generally include a limited number of patients.

Also, the methods of regulation, dosage regimen and follow-up of the antidepressant treatment must be identical to the recommendations indicated in the marketing authorizations (MA) of the corresponding specialities:

As a reminder:

- all antidepressants can induce manic mood changes, particularly in bipolar patients. The care of these patients requires the opinion of a specialist.
- benzodiazepines or similar molecules should not be systematically associated with antidepressants.

Safety profile of antidepressants

SSRIs and SNRIs are associated rarely with an increase in hepatic enzymes, and more rarely with hepatitis, whose course is generally favourable on discontinuing the treatment. For this reason, they must be used with care in patients with hepatic insufficiency and even more so in patients infected by HCV. The possible role of antidepressants in the appearance or the progression of hepatic disorders must be considered. The data currently available are insufficient to enable any formal classification of antidepressants according to their hepatotoxic potential. However, duloxetine (Cymbalta®), a recently marketed product, should not be used in a context of a viral hepatitis, because of its hepatotoxic risk. Indeed, this antidepressant is contra-indicated in patients with liver disease resulting in hepatic impairment.

Depression is associated with the risk of suicidal thoughts, suicide attempts and completed suicide which must be taken into account throughout the treatment by antidepressant and until obtaining significant remission. The occurrence or the worsening of depressive symptoms, insomnia, irritability, anxiety, and signs of impulsiveness and aggressiveness should lead to more frequent consultations.

All antidepressants have the potential of inducing an inversion of mood with the appearance of hypomanic or manic symptomatology. In this case, the antidepressant treatment must be stopped and the management of the patient performed in liaison with a psychiatrist.

The risk of bleeding connected with SSRI and SNRI must be taken into account and monitored in patients infected by HCV. Indeed, this can be raised because of the haematological abnormalities (thrombopaenia) caused by chronic hepatitis C (in particular in the event of cirrhosis) or following the administration of interferon alfa.

In rare cases, a serotonin syndrome or a clinical picture of neuroleptic malignant syndrome can occur during treatment by SSRIs and SNRIs, particularly when these are associated with serotonergic and/or antipsychotic drugs.

Concerning mianserin (Athymil®) and mirtazapine (Norset®):

There is no reliable data evaluating the efficacy and safety of mianserin and mirtazapine in depression related to treatment by interferon alfa. In the event of their use in this context, the haematological toxicity of these antidepressants must be taken into account.

Duration and discontinuation of treatment:

Adverse psychiatric effects have been reported after discontinuing anti-hepatitis C treatment and particularly in the six following months.

Consequently, if the treatment by antidepressants is well tolerated and effective, it should be maintained throughout anti-hepatitis C treatment and for four to six months after discontinuation treatment. However, in the case of a patient with a history of depression (recurrent depression), it may be necessary to prolong the antidepressant treatment, and in this case a specialized opinion is called for. The discontinuation of the antidepressant must take place progressively in order to limit the risk of withdrawal syndrome. The patient should be warned of the potential risk of relapse and be informed of the need to consult quickly in the event of reappearance of the signs.

» Manic and hypomanic episodes

Given that liver toxicity is not part of the safety profile of these products, lithium salts are the preferred mood stabilizer in patients infected by HCV. It should be noted, however, that lithium salts can disturb thyroid function and for this reason, an assessment of thyroid function must be performed before beginning the treatment. Any hypothyroidism has to be corrected. The potentiation of these effects in the event of the association with interferon alfa is unknown.

The risk of the appearance of a serotonin syndrome in the event of the association of lithium with SSRIs and SNRIs must also be taken into account.

Considering the hepatotoxic risk of carbamazepine, this drug should not be used in patients infected by HCV.

Antipsychotics such as olanzapine and risperidone can be used in the treatment of moderate to severe manic episodes. However, disturbances of the hepatic profile have frequently been observed particularly at the beginning of treatment by olanzapine. Caution should therefore be exercised in patients with a hepatic insufficiency or a disturbance of the hepatic profile before the introduction of this treatment.

» Isolated behavioural problems

The occurrence of behavioural problems such as irritability, impulsiveness, aggressiveness, or hyperactivity in a patient infected by HCV and treated with interferon alfa should encourage the doctor to look for the presence of other associated psychiatric disorders, particularly a hypomanic or manic episode and/or concomitant consumption of drugs which would require a specialized opinion.

3. Patient drug management in special populations

» Patients co-infected with HCV and HIV (Human Immunodeficiency Virus)

In HCV-HIV co-infected patients, the psychotropic drugs chosen should not interfere or only interfere minimally with the antiretroviral treatment particularly if this includes ritonavir which is a potent inhibitor of P450 cytochrome. In addition, it should be noted that the association of ritonavir and methadone can reduce plasmatic concentrations of methadone. This association therefore requires regular clinical monitoring and possibly adaptation of methadone dose regimen.

» Patients receiving methadone

Patients stabilized by methadone for whom treatment includes pegylated interferon alfa 2a or alfa 2b should be monitored in order to detect possible signs or symptoms of methadone toxicity because plasmatic concentrations may increase.

Methadone should be administered with care and clinically, electrolytically and electrocardiographically monitored in patients at risk of QT interval prolongation, particularly in the event of high doses of methadone or association with drugs known to prolong QT interval such as certain antipsychotics.

In addition, fluvoxamine (SSRI) increases the plasmatic concentrations of methadone (by reducing its hepatic metabolism) and this can lead to signs of overdose. The clinical and electrocardiographic monitoring should be reinforced and if necessary, the methadone dosage regimen should be adjusted during the treatment by the antidepressant and after its discontinuation.

III- Following anti-hepatitis C treatment

Depressive episodes with suicidal ideation, suicide attempts and completed suicide as well as hypomanic or manic episodes have been reported several months after discontinuing anti-hepatitis C treatment and particularly during the six months after discontinuation. The risk appears greater however during the first four weeks following the discontinuation of interferon alfa. It is therefore advisable to continue close monitoring of the psychiatric state of the patient even after discontinuation of the anti-hepatitis C treatment. In the event of treatment by antidepressant, it is recommended to maintain the treatment for four to six months following the discontinuation of the anti-hepatitis C treatment. However, in the case of a patient having a history of depression (recurring depression), it may be necessary to prolong the treatment by antidepressant, and this requires a specialized opinion.

The patient, his attending doctor and his close relatives should be informed of the possibility of the occurrence or aggravation of psychiatric disorders after discontinuation of the anti-hepatitis C treatment, of the potential risk of the reappearance of signs after discontinuation of the treatment by antidepressant and the need to consult quickly if such disorders are observed.

APPENDIX

MODULES OF MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (M.I.N.I)

A. MAJOR DEPRESSIVE EPISODE				
A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES	1
A2	In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time ?	NO	YES	2
	A1 OR A2 SCODED YES ?	➔ NO	YES	
A3	Over the past two weeks, when you felt depressed and/or uninterested :			
a	Was your appetite decreased or increased nearly every day or did your weight decrease or increase without trying intentionally ? (i.e., $\pm 5\%$ of body weight or $\pm 3,5$ kg or ± 8 lbs., for a 70 kg / 120 lbs. person in a month) IF YES TO EITHER, CODE YES	NO	YES	3
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening, or sleeping excessively)?	NO	YES	4
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still, almost every day?	NO	YES	5
d	Did you feel tired or without energy, almost every day?	NO	YES	6
e	Did you feel worthless or guilty, almost every day?	NO	YES	7
f	Did you have difficulty concentrating or making decisions, almost every day?	NO	YES	8
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES	9
A4	ARE 3 OR MORE A3 ANSWERS CODED YES? (OR 4 A3 ANSWERS IF A1 OR A2 ARE CODED NO) IF PATIENT MEETS CRITERIA FOR MAJOR DEPRESSIVE EPISODE CURRENT :	NO YES Major depressive Episode current		
A5a	During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about?	➔ NO	YES	10
b	Was there an interval of at least 2 months without depression and/or lost of interest between your current episode and your last episode of depression?	NO	YES	11
	IS A5b CODED YES?	NO YES Major depressive Episode past		

C. SUICIDALITY																
In the past month did you :																
C1	Think that you would be better off dead or wish you were dead?	NO	YES	1												
C2	Want to harm yourself?	NO	YES	2												
C3	Think about suicide?	NO	YES	3												
C4	Have a suicide plan?	NO	YES	4												
C5	Attempt suicide?	NO	YES	5												
C6	In your lifetime, Did you ever make a suicide attempt?	NO	YES	6												
IS AT LEAST 1 OF THE ABOVE CODED YES?		<table border="1"> <thead> <tr> <th>NO</th> <th>YES</th> </tr> </thead> <tbody> <tr> <td colspan="2">Suicide risk</td> </tr> <tr> <td colspan="2">Current</td> </tr> <tr> <td>Low</td> <td><input type="checkbox"/></td> </tr> <tr> <td>Moderate</td> <td><input type="checkbox"/></td> </tr> <tr> <td>High</td> <td><input type="checkbox"/></td> </tr> </tbody> </table>			NO	YES	Suicide risk		Current		Low	<input type="checkbox"/>	Moderate	<input type="checkbox"/>	High	<input type="checkbox"/>
NO	YES															
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IF YES, SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS :																
C1 or C2 or C6 = YES : LOW																
C3 or (C2 +C6) = YES : MODERATE																
C4 or C5 or (C3 + C6) = YES : HIGH																

D. (HYPO) MANIC EPISODE				
D1a	Have you ever had a period of time when you were feeling «up» or «high» or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY «UP» OR «HIGH», CLARIFY AS FOLLOW : By «up» or «high» I mean : having elated mood, increased energy, needing less sleep, having rapid thoughts, being full of ideas, having an increase in productivity, creativity, motivation or impulsive behavior.	NO	YES	1
b	IF YES Are you currently feeling «up» or «high» or full of energy ?	NO	YES	2
D2a	Have you ever been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? (Do not consider times when you were intoxicated on drugs or alcohol)	NO	YES	3
b	IF YES Are you currently feeling persistently irritable?	NO	YES	4
ARE D1a OR D2a CODED YES?		→ NO	YES	

D3	IF D1b OR D2b = YES : EXPLORE ONLY CURRENT EPISODE IF D1b AND D2b = NO : EXPLORE THE MOST SYMPTOMATIC PAST EPISODE											
	During the time(s) when you felt «high», full of energy and/or irritable did you:											
a	Feel that you could do things others couldn't do, or that you were an especially important person?	NO	YES	5								
b	Need less sleep (e.g., feel rested after only a few hours sleep)?	NO	YES	6								
c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES	7								
d	Have thoughts racing?	NO	YES	8								
e	Become easily distracted so that any little interruption could distract you?	NO	YES	9								
f	Become so active or physically restless that others were worried about you?	NO	YES	10								
g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (e.g., spending sprees, reckless driving, or sexual indiscretions)?	NO	YES	11								
	ARE 3 OR MORE D3 ANSWERS CODED YES OR 4 IF D1a = NO (PAST EPISODE) OR D1b = NO (CURRENT EPISODE)?	→ NO	YES									
D4	Did these symptoms last at least a week and cause significant problems at home, at work, or at school, or were you hospitalized for these problems? IF YES TO EITHER, CODE YES	NO	YES	12								
	IS D4 CODED NO ? IF YES, SPECIFY IF THE EPISODE EXPLORED IS CURRENT OR PAST	<table border="1"> <tr> <td>NO</td> <td>YES</td> </tr> <tr> <td colspan="2">Hypomanic episode</td> </tr> <tr> <td>Current</td> <td><input type="checkbox"/></td> </tr> <tr> <td>Past</td> <td><input type="checkbox"/></td> </tr> </table>			NO	YES	Hypomanic episode		Current	<input type="checkbox"/>	Past	<input type="checkbox"/>
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