CHAPTER 21

Mental Health and Hepatitis C

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SECTION 2

Mental Health Issues During Interferon-Based Therapy

Introduction

Most people are aware that the significant benefits of *interferon-based therapy* to treat *chronic hepatitis* C virus (*HCV*) may cause a variety of physical side effects (*see Chapter 8, Western (Allopathic) Medicine*). It is important to be aware that this treatment may also have emotional and mental health side effects.

Approximately 20% to 30% of people undergoing interferon-based therapy for hepatitis C experience *depression*. By being aware of this possibility, you are more likely to recognize the *symptoms* early, request one of the many antidepressant (or mood stabilizing) medications available to treat it, and feel better for the remainder of the treatment period. Although most people do not become depressed during HCV treatment, the depression that does occur is not just a result of adjusting to the changes in your life associated with undergoing treatment. Researchers have recognized for years that interferon-based therapy for HCV can itself cause depression.[1]

While the depressive symptoms caused by interferon-based therapy usually improve as soon as the medication is stopped, this depression also responds well to antidepressant treatment during HCV *antiviral* therapy. Getting help for depression while on interferon-based therapy will prevent early discontinuation of this potentially life-saving course of HCV treatment. This chapter is intended to help you prepare mentally and emotionally for the decision to start HCV treatment. Preexisting mental health or substance use disorders are common among people with HCV and should not be used as reasons for exclusion from treatment.

However, if you have a current psychiatric disorder or are abusing drugs or alcohol, you should consider seeking treatments for these problems — if possible, before you start treatment for HCV. There are many reasons to get clean and sober that are specifically related to HCV infection. Waiting to start HCV treatment can actually serve as an effective motivator to achieve *abstinence* and sobriety, even if that has been difficult for you in the past. In the meantime, continue to discuss the risks and benefits of HCV treatment with your with your healthcare providers.

The most important question is not when to start your treatment for HCV, but when you feel ready to make the commitment to complete it once you start.

Later in this section, you will find some of the ways you can try to prevent, minimize, or treat the mental or emotional side effects of HCV treatment. There is also a discussion of some of the research on the effect of HCV and its treatment on your quality of life, or as researchers call it, "health-related quality of life" (HRQOL).

People tend to tolerate side effects better and can identify them earlier if they know about them in advance, so be sure to discuss these with your healthcare providers until you are sure you understand them.

This chapter will primarily focus on depression and its treatment because it is by far the most common psychiatric side effect of *pegylated interferon* plus ribavirin treatment. Other potential psychiatric side effects will also be discussed.

In the midst of discussing all of these possible side effects of pegylated interferon plus *ribavirin* treatment, it is important not to lose sight of the "goal." The goal is to get the maximum benefit from your pegylated interferon plus ribavirin therapy, that is, achieving a *sustained viral response* (*SVR*) by clearing the virus from your body, reversing *fibrosis* in your liver, and decreasing the chance of developing *liver failure* and/or *liver cancer*.[2]

My "goal" in this section is to help you do what you can to be mentally prepared so you can do your part by taking the medications as prescribed, following up with appointments, and creating a working partnership with your healthcare providers.

Interferon-based therapy can be emotionally and physically challenging.
Remember… Keep your eye on the prize!

Words of Caution About Drawing Conclusions From Current Research

Anyone with HCV who is trying to understand the mental health aspects of pegylated interferon plus ribavirin treatment should be briefly warned about three different issues that can be confusing when you hear or read about research discussing psychiatric disorders and HCV therapy.

First…

People with HCV have a higher proportion than the general population of preexisting psychiatric disorders and substance abuse disorders, especially if they have a past history of intravenous drug use as a risk factor for HCV. This means that these psychiatric disorders, including mood disorders, predate their treatment for HCV and usually predated their HCV.

During pegylated interferon treatment, however, people who have never had a psychiatric disorder may still experience significant depression directly induced by the pegylated interferon. Further, people with stablized preexisting psychiatric disorders prior to beginning interferon-based therapy may experience a recurrence or worsening of their symptoms, or experience a *relapse* of their substance use disorder during HCV treatment.

If you have had a prior history of depression or another mood disorder (for example, bipolar disorder), studies vary regarding whether you are at higher risk for depression during interferon-based therapy. One study found that half of those with histories of depression had a recurrence during treatment, and half did not.[3] However, if you are depressed or even "subclinically depressed" (meaning the symptoms are severe enough to warrant immediate treatment with antidepressant medication) at the time you start interferon-based treatment, you are still at increased risk for *clinical* depression that may require antidepressant medication during your HCV therapy.[4] In some cases, you may want to consider preventive measures, something discussed later in this section.

Second…

You may hear about results from a variety of research related to interferon or interferon-alfa. But the research that is most pertinent to you is likely to be more recent research about pegylated interferon plus ribavirin, the current standard of care for the treatment of chronic hepatitis C.

And A Final Note of Caution…

Discussions of rates and consequences of depression as a side effect of pegylated interferon plus ribavirin treatment for HCV are based on research that varies significantly in the way "depression" has been measured. Various methods of evaluation can sometimes result in conflicting and often confusing differences in their conclusions. This is a major reason

why what you hear about depression and other psychiatric side effects of interferon-based treatment for HCV may not be consistent across studies.

So be cautious in drawing conclusions from studies you may hear about or read because the rates of people experiencing depression that are reported before or during HCV treatment may vary depending on how the depressive symptoms are evaluated.

On the other hand, it usually doesn't help most people to avoid learning about the side effects of HCV treatment. You are likely to feel more in charge of your treatment if you learn more about it. If your healthcare provider gives you a periodic self-rating scale as a means of monitoring you for side effects, be sure to take the time to fill it out accurately. However, if you become aware of feeling more depressed or no longer finding pleasure in anything, you may recognize these symptoms before your healthcare providers because you have learned to monitor them for yourself and you should take an active role in getting treatment or requesting a psychiatric evaluation.

Importance of Knowing About Depression and Other Possible Psychiatric Side Effects of Pegylated Interferon Plus Ribavirin Treatment

Despite the cautions I just gave you about research related to the psychiatric side effects of interferon-based therapy, these potential psychiatric side effects are still important to consider for a number of reasons:

- There is a 20% to 30% chance that you may experience significant depression during interferon-based therapy, even if you have never been diagnosed with depression before.[5]
- Psychiatric side effects are the most common reason for early discontinuation or reduction in medication dosage during HCV treatment.[6]
- Psychiatric side effects of interferon-based therapy such as mania or suicidal thoughts may require emergency intervention, treatment, and possibly psychiatric hospitalization, in addition to immediate discontinuation of HCV treatment.[7]
- Most importantly, most psychiatric side effects of pegylated interferon treatment are treatable. A variety of antidepressant (or mood stabilizing medications) are very effective and can help you feel much better during the entire course of your HCV treatment.

People with severe psychiatric side effects from interferon-based therapy have sometimes unnecessarily discontinued their treatment because they felt so discouraged about their quality of life during treatment, or so depressed as a result of it. Or it may have been discontinued prematurely in the past by their healthcare providers out of concern that they not get worse. Now you and they know that these side effects can be treated, and early discontinuation of HCV treatment or dose reductions are usually not necessary.

You are likely to feel better about your treatment and yourself if you take an active role by:

- learning as much as you can about the treatment before you start it
- knowing what potential side effects to watch out for
- communicating with your healthcare providers about your experiences

Stabilizing Psychiatric and Substance Abuse Disorders Before Starting HCV Treatment

You can begin to prepare yourself mentally and emotionally for HCV treatment by being sure that when you are ready to make the decision to start it, you are also ready to follow through and complete the treatment — so you will get the full benefit from it. If you have a current psychiatric condition, or an alcohol or substance use disorder, consider getting a psychiatric evaluation or enrolling in a substance treatment program to get clean and sober.

For example, if you have a history of one or more episodes of a "major depressive disorder" that has required antidepressant medication in the past, and you are feeling depressed, hopeless, tearful or not finding pleasure in anything, you should consider consulting with a psychiatrist or asking your healthcare provider to restart antidepressant medication.

In the meantime, you should discuss your individual risks and benefits of HCV treatment with your healthcare providers in order to be a full participant in the important decision about when you are ready to start the treatment. You will likely consider your liver enzymes, your genotype, and the *stage* of disease in your liver in light of your past treatment history. (See *Chapter 8, Western (Allopathic) Medicine* for additional information.)

Prior to the 2002 Consensus Statement on the Treatment of HCV from the National Institutes of Health[8], HCV-infected individuals with associated psychiatric and substance use disorders were often unnecessarily excluded from HCV treatment, and there have been discussions about whether this was ethical.[9] While it is advantageous for these disorders to be evaluated and stabilized before HCV treatment, they should not prevent anyone from being eligible for *antiviral* treatment on the basis of that history alone.

Excluding individuals with psychiatric and substance use disorders from HCV treatment has been justified historically because of the assumption of decreased adherence and follow-up with treatment.[10] But research suggests this is not a valid assumption. This is an important question for a large segment of the HCV-infected population. For example, up to 85% of HCV-infected veterans also have psychiatric and substance use disorders.

While there are few large studies separating preexisting from current psychiatric and substance use disorders among HCV-infected individuals, one review of the medical records of 1.9 million veterans between 1992 and 1999 found that 1.77% were HCV-infected. Among those with HCV, 85% had a past history of psychiatric or substance use disorders, 31% had an active psychiatric or substance use disorder, most frequently cocaine (69%) and opiates (48%). Among those with comorbid disorders (that is, both psychiatric and substance use disorders), 85% had depression, 71% had anxiety disorders, 43% had posttraumatic stress disorder, 42% had psychotic disorders, and 30% had bipolar disorders.[11]

A recent review of the records of 294 HCV-infected veterans with psychiatric and substance use disorders compared to 353 controls found that the former group was more often considered ineligible for treatment for HCV, and were treated less frequently despite comparable viral and liver characteristics.[12] These researchers found that rates of HCV therapy completion rates and SVR were similar between the groups.

Most clinicians now recommend a case-by-case, individualized risk-benefit assessment between you and your healthcare providers to make the decision about when to start HCV treatment. You should not accept being told you are ineligible simply because you have a preexisting psychiatric or substance use disorder. But it is likely to be to your advantage to seek treatment before starting HCV therapy.

If you feel ready not just to start, but to complete the treatment, be sure to let your healthcare providers know, even if they have not yet started that discussion with you.

Intravenous Drug Use and HCV

The most common exposure to the hepatitis C virus is through intravenous drug use. The figures that are often cited are alarmingly high: 50% to 80% of intravenous drug users become HCV-infected after one year of drug use, and nearly all become infected after eight years of use.[13] However, a more recent study in New York[14] suggests that HCV prevalence declined from 80% to 59% among HIV-negative individuals and from 90% to 63% overall between 1990 and 2001. The authors felt this was attributable to the availability of needle exchange programs. Their estimated HCV incidence in 2000 to 2001 among new injectors was 18 per 1,000 person-years at risk.

The 1997 NIH Consensus statement[15] recommended that people who use illicit drugs not be offered HCV treatment until they had been abstinent for at least six months. One academic group[16] has argued that the four reasons used to justify this guideline - expectations of decreased adherence, increased side effects of treatment, risk of reinfection, and the fact that the timing of treatment should allow for a period of abstinence before starting HCV treatment - are not valid in routinely denying treatment to illicit drug users. They also argue that treatment decisions should be individualized on

the basis of evidence-based risk-benefit considerations, and augmented by substance treatment programs (including needle exchange programs), establishing increased trust in the doctor-patient relationship, and providing close monitoring of side effects of HCV treatment and relapse behavior.

There have been a number of studies of people who use intravenous drugs (IDUs) and the impact of depressive symptoms or a period of abstinence prior to HCV treatment on their completion of treatment. One Italian study[17] found that the presence of depressive symptoms among IDUs before or during pegylated interferon plus ribavirin treatment did not affect their virologic response or predict early treatment discontinuation. However, the presence of other physical side effects did increase the likelihood of early treatment discontinuation, and they encouraged healthcare providers to address these physical side effects as soon as they were identified in order to promote higher rates of treatment completion, rather than making a large group ineligible for treatment or allowing early discontinuation.

Another study from San Francisco[18] found that among 76 recovering heroin users on methadone, 28% had a sustained viral response and 24% discontinued treatment early. Neither drug use during HCV treatment nor a short duration of pretreatment drug abstinence diminished the virologic outcomes.

So people should not be excluded from HCV treatment because of their substance abuse. But there are many reasons to get clean and stay clean before HCV treatment. For example, there have been important questions raised about whether ongoing opiate dependence may negatively affect the outcome of HCV treatment by enhancing viral replication, liver injury, and hepatic fibrosis.[19] These authors suggest that being on methadone is not a contraindication to HCV treatment, but should be further studied in this regard.

The two substitution therapies for opiate dependence, methadone and buprenorphine, promote harm reduction and may help HCV-infected individuals stabilize their abstinence before HCV treatment (see *Chapter 20, Interferon-Based Therapy in Recovery*). Patients on methadone may continue on their usual doses with stable chronic liver disease, including advanced *cirrhosis*. Buprenorphine is another substitution therapy that may be administered directly by physicians who have received training and certification, in contrast to the highly regulated methadone maintenance treatment programs. However, patients should be warned that attempts to abuse it can cause liver dysfunction after sublingual and especially after intravenous administration.[20]

Despite the fact that people who are using intravenous drugs often feel that they have “many strikes against them,” being able to start interferon-based therapy may be a great motivator. The possibility of clearing HCV from their body, and especially, helping them feel better on a daily basis, can be a powerful force for major changes in their lives. Many people find that they can start a new chapter in their life book. If you are using intravenous drugs, you are likely to do better with an organized treatment program, but the hepatitis C virus may give you the challenge you need not only to make the decision to stop using, but to stay clean.

Alcohol Dependence and HCV

People with histories of alcohol abuse and alcohol dependence have a rate of HCV infection that is double that of the general population, even when individuals with other HCV risk factors are excluded.[21] It is possible that intranasal cocaine use and sharing of cocaine “straws”, or tattooing by friends are additional risk factors for HCV among these individuals who have never used intravenous drugs.

There are many reasons to get sober and stay sober before starting HCV treatment. Median daily alcohol use of more than 30 grams is associated with failure to respond to interferon-based treatment for HCV, despite a period of abstinence before starting treatment.[22] Individuals with chronic hepatitis C who continue to use alcohol are two to three times more likely to develop cirrhosis and associated complications, and HCV-infected patients admitted to the hospital with alcohol-related diagnoses have longer hospital stays and are more likely to die in the hospital.[23]

Alcohol decreases the cellular effects of interferon, increases HCV *viral load*, reduces the virologic response to HCV treatment, and accelerates the progression of fibrosis in the liver. For all these reasons, some authors suggest that the potential liver *toxicity* from disulfiram (Antabuse®) is likely to be lower in people with HCV than the toxicity from alcohol, despite the fact that this has not been studied directly. Disulfiram (Antabuse®), monitored Antabuse®, or acamprosate

(Campral®) can be effective in helping you maintain sobriety. A 12-step program such as Alcoholics Anonymous is often successful in helping people stop drinking. (See *Chapter 3, Alcohol and Hepatitis C* for additional information.)

In one 28-day substance treatment program for alcohol and other substance dependence (without IDUs), 23.1% were HCV-infected, and those who completed the substance treatment program were more likely to receive HCV treatment than HCV-positive individuals who had never been in a substance treatment program. These authors[24] report that as part of their treatment program, they educated people about HCV and its treatment, tested them for HCV, and told people at the beginning of the treatment program that they would only be eligible for treatment if they remained abstinent. Almost 90% of the HCV-positive participants completed the program and had a planned discharge versus 67% of the HCV-negative group. Forty-nine percent of HCV-positive participants were abstinent six months after program completion compared to 31% of the HCV-negative individuals. The association between HCV positive status, program completion, and sobriety at six months was statistically significant. HCV-infected participants were more likely to complete the substance treatment program and remain abstinent for 6 months after program completion than the other program participants who were not HCV-infected.

This suggests that a desire to get HCV treatment can be a powerful motivator for remaining clean and sober when people are educated about HCV and its major risks to health over a lifetime. It is also a reminder that you will probably have a better chance of getting clean and sober with the support and structure a formal substance treatment program. But you will know what works best for you.

Severe Mental Illness and HCV

Five percent to 7% of adults in the United States have a severe mental illness. Half of all people with a severe mental illness also have a substance use disorder and are at increased risk for HCV and HIV. From 1997 to 1998, one group studied coinfection with HIV, hepatitis B and HCV in a multisite sample of 755 patients with severe mental illness. They found that 14.4% were positive for HCV, 3% were positive for HIV, and 1.7% were coinfected with both HIV and HCV. Coinfection in this very vulnerable population was associated with psychiatric illness severity, ongoing drug abuse, poverty, homelessness, incarceration, urban residence and minority status.[25]

Of note, HCV monoinfected individuals continued to engage in behaviors that are high risk for HIV. Studies suggest that while people with severe mental illness tend (on average) to be less sexually active, those who are sexually active tend to engage in more behaviors that are high risk for HIV[26], and possibly HCV. It is likely that HCV treatment programs for the most severely mentally ill populations will need to incorporate concrete services such as help with access to housing, public assistance programs, and education about high risk behaviors.

People who are HIV-positive and are coinfected with HCV are another undertreated population. Success rates with pegylated interferon plus ribavirin treatment are for HCV/HIV coinfection are more modest than seen with HCV infection alone. In one study of HCV/HIV coinfected individuals, 90% had access to primary medical care, but only 21% were referred to a specialist for evaluation of their HCV, and less than 4% were treated with interferon-based therapy.[27] Compared with HCV uninfected individuals, HCV co-infected patients were more likely to be using injection drugs, to be homeless for more than one year, and to be actively depressed.

In summary, there is generally little to lose and a lot to be gained by waiting to start HCV treatment until you have sought treatment to stabilize any psychiatric disorders and to get clean and sober. You will not be able to clear HCV from your body if you relapse with drugs, alcohol, or psychiatric symptoms and have to stop therapy. You can maximize the chance of a good treatment outcome by remaining clean and sober during treatment.

However, if you do relapse or have a recurrence of psychiatric symptoms during HCV treatment, let your healthcare providers know so you can get treatment as soon as possible. If the HCV treatment needs to be discontinued, it should be possible to restart once your symptoms have been stabilized. However, remember that whenever you do make the decision to start HCV treatment, make the decision to finish it as well.

Health-Related Quality of Life and Physical Side Effects of Interferon-Based Therapy

Historically, chronic hepatitis C had been considered an asymptomatic illness (meaning without significant symptoms).[28] However, there have been a number of studies[29-31] that focus on measures of "health related quality of life" (HRQOL), and it has been demonstrated that people living with chronic hepatitis C have a lower HRQOL than others without it, independent of the present of cirrhosis.[32] While these studies were largely done during the era of standard interferon plus ribavirin treatment, they suggest significant reductions in physical function[33] that impact the HRQOL for HCV-infected individuals even before starting interferon-based therapy.

Researchers use several standardized measurements to compare the effects of different illnesses on the quality of life of people living with them.[34] For example, there is a greater effect in lowering the HRQOL in individuals with chronic hepatitis C than among people with chronic hepatitis B.[35] The magnitude of decrease in HRQOL is at least as large as other chronic diseases such as diabetes mellitus and chronic arthritis.

While the once weekly schedule of pegylated interferon has reduced the intrusion of this treatment in the course of people's lives, the physical side effects during a lengthy treatment course on pegylated interferon may make some people feel worse before they feel better. Reflecting this experience, researchers have found that the HRQOL for people on pegylated interferon tends to decline after 12 to 24 weeks of treatment, but then generally returns to baseline.[36] Both fatigue and depression tend to improve at the conclusion of pegylated interferon treatment.

The following are the percentages of some of the physical side effects of pegylated interferon alfa-2a plus ribavirin treatment that were reported from one of the major pegylated interferon treatment studies, involving 1,121 patients at multiple sites.[37] The side effects listed are common and are among those that can particularly affect your quality of life. Decreased interest in sex can also occur with pegylated interferon treatment, perhaps as a result of a combination of the other side effects. It is included here, although it was not originally reported in this study.

- fatigue 54%
- headache 47%
- insomnia 37%
- nausea 29%
- decreased appetite 21%
- decreased interest in sex

Remember that no one experiences all the side effects of any medication, and some people don't experience any. Many of these can also be decreased or improved by other treatments. For a more detailed discussion of the potential side effects of pegylated interferon treatment, refer to *Chapter 8, Western (Allopathic) Medicine*.

One study of fatigue and HRQOL found that scores were not as impaired on pegylated interferon as with standard interferon in the realms of physical or emotional role limitation, general health, vitality, and social function.[38] But it will take more studies to know if the effects of pegylated interferon are different from standard interferon on the quality of peoples' daily lives. More reassuring, while not surprising, is the finding that HRQOL measures improve among patients even before they knew they had achieved an SVR.[39]

As with any medical illness, people differ in the way they respond to the demands of the treatment they require for that illness. Some experience the treatment itself - such as the need for multiple medical appointments, getting blood tests, taking or self-administering medications, and medication side effects - as an additional burden of the illness. Others look to the treatment as a possible salvation from their illness and consider the demands of that treatment a passing phase on the way to recovery or cure.

Symptoms that are considered "reactive" or in response to the demands of treatment or the symptoms of the illness are considered "adjustment" issues and usually do not require treatment with psychiatric medications. Often, psychotherapy or counseling can be very beneficial for reactive symptoms. For example, someone who experiences fatigue and decreased interest in sex may benefit more from a few couples sessions with a therapist (who can facilitate communication about the effects of the illness on both the patient and the partner) than from a course of antidepressant medications.

While ribavirin may have a role in side effects such as insomnia (37% on pegylated interferon with ribavirin and 23% without ribavirin) and decreased appetite (21% on pegylated interferon with ribavirin and 11% without ribavirin)[40], one well known side effect of ribavirin affecting HRQOL is anemia. Many people on pegylated interferon plus ribavirin experience significant fatigue because they are anemic from the ribavirin.

In a Swedish study[41], patients who had a fall of more than 20% of their hemoglobin levels were significantly lower in measures of HRQOL than those who had decreases in hemoglobin of less than 10%. While treatment-related anemia is often taken care of by decreasing the ribavirin dose, people who experience fatigue related to anemia will often experience more energy and a higher quality of life after treatment with erythropoietin. This may be an option to explore with your healthcare provider.[42]

One study found that while fatigue and depression both negatively affect the HRQOL of people on combination therapy, the effect of depression far outweighed the effect of fatigue or any other side effect on the HRQOL in the experience of most patients.[43] Another study of 271 patients found that although both anemia and depression were associated with impairment in HRQOL, but depression was the "most consistent predictor."

Some studies suggest that patients who take on physical symptoms and the experience of illness as a "challenge" (as opposed to another unfortunate effect of the illness that must be accepted, or even as a punishment) tend to cope better overall.[44] Not only do many patients feel they just "need to be strong" and accept difficult side effects, many healthcare providers feel that it is "understandable" and "natural" that people with HCV might feel depressed. This can cause both patients and providers not think as actively as they could about using treatments to intervene when side effects occur to help people feel better.[45] You may need to be the one to activate such interventions.

You can have an active role in decreasing the impact of these side effects on the quality of your life by learning about them. In learning about possible side effects, you will be prepared to tell your healthcare providers if they occur. You can request the treatments to minimize any side effects you may experience instead of just trying to accept them as another burden of the illness. In addition, by learning as much as you can about this illness, its treatment, and possible side effects, you may experience improved self-esteem by feeling "empowered" and advocating for yourself. Knowing more about your situation may make it more likely that you will find ways to feel better!

Psychiatric Side Effects and Interferon-Based Therapy

Psychiatric side effects of interferon-based therapies for HCV include depression, mania, psychosis, suicidal thoughts, and anxiety. There are no consistent predictors of who will develop these disorders as side effects of interferon-based therapy, even among those with clear histories of preexisting psychiatric disorders.

In a study of people receiving interferon-based therapy who had preexisting psychiatric disorders (but were not in psychiatric care at the beginning of interferon-based treatment), ½ did not require any psychiatric intervention or develop significant psychiatric symptoms during the treatment. The only two factors that seemed to be associated with progression to frank psychiatric symptoms during interferon-based therapy were a family history of psychiatric disorders and having more than one psychiatric disorder at baseline.[46]

Depression on Interferon-Based Therapy

Many studies have documented the occurrence of depression during standard interferon and standard interferon plus ribavirin treatment for HCV.[47-49] Depression occurred in 20% to 30 % of patients in these studies.[50] There have been fewer studies investigating the effects of pegylated interferon on mood.

The previously cited study of 1,121 subjects from 81 sites[51] found lower rates of depression (20% and 22%) among patients treated with pegylated interferon compared to those treated with standard interferon (30%). This is a particularly significant percentage since the baseline rate of both a history of depression and active depression was very low for this sample (less than 5%). Notably, psychiatric side effects (mostly events related to depression) were still the most common reasons for early discontinuation of treatment.

However, not all studies have noted this difference between standard interferon and pegylated interferon. A study conducted in Germany[52] compared psychiatric side effects in 48 patients who were treated with standard interferon and 50 patients who were treated with pegylated interferon. They found the rates of depression between the two groups were not statistically different. Furthermore, measures of HRQOL (primarily depression and anger/hostility) were similar in the two groups.

Notably, while major depressive disorders are consistently found to be twice as common in women as in men in the general population, most studies have found that men and women are equally at risk for becoming depressed as a result of the pegylated interferon plus ribavirin treatment.

Finally, one study stressed the importance of identifying and treating depressive symptoms because their results suggested that people who experience significant depressive symptoms on interferon-based therapy may be less likely to clear HCV.

Fortunately, depressive symptoms related to interferon-based therapy respond well to antidepressant medication so be sure to consider asking for it — and feel better.

Mania and Irritability on Interferon-Based Therapy

A French study[53] of 93 patients treated with pegylated interferon-alfa 2b plus ribavirin reported "psychiatric events" or side effects in 32% of their sample. The mood disorders were diagnosed as follows: mania (10%), irritable hypomania (50%) and depressive mixed states (40%). Three patients in that study exhibited classic euphoric manic symptoms and there is another extensive case report of mania that arose during pegylated interferon plus ribavirin treatment.[54] In a study of 943 patients on standard interferon, one of the 43 patients who developed psychiatric symptoms was manic.[55]

The development of frank manic symptoms (such racing thoughts, grandiose thoughts, extreme irritability, hypersexuality, hyperactivity, and decreased need for sleep) with or without psychotic symptoms requires emergency intervention, discontinuation of interferon treatment, and the immediate initiation of psychiatric treatment.

The French study highlights the question of how to consider irritability, anger, and hostility in the diagnosis of depression versus bipolar depression. This is important for several reasons. Irritability is very common during the course of HCV treatment. Many patients with irritability on interferon-based therapy reportedly show improvement with antidepressant medication. However, patients with significant irritability and depression who are diagnosed with a bipolar disorder are usually treated with a mood stabilizer, and are considered at risk for deterioration if incorrectly treated with antidepressants. Several papers have discussed these issues in detail.[56, 57] In general, a psychiatrist should be consulted if there is a question about diagnosis or treatment.

People who are manic or especially "hypomanic" (where manic symptoms are not as fully symptomatic) may, understandably, not want to let go of those feelings as they are experienced as positive and/or pleasant. But the problem is that these feelings and thoughts always "spin out of control" and result in impaired judgment that can end up being highly self-destructive. As illogical as it may seem, if you feel "on top of the world" and it is "too good to be true," it probably is. You may be manic and need psychiatric treatment.

Suicidal Thoughts on Interferon-Based Therapy

A survey of 15 hospitals from 10 countries estimated one patient in 5[15] on standard interferon treatment developed suicidal thoughts, and these were not preceded by prior histories of suicide attempts.[58]

While very few suicides have been reported among HCV patients on alfa interferon therapy[59, 60], it is critical to identify anyone with suicidal thoughts or feelings. People with a sense of hopelessness beyond depression, and those actively making plans to take their own lives are at highest risk for actual suicide attempts. Suicidal thoughts with active intent are always an emergency and require immediate psychiatric intervention and discontinuation of the pegylated interferon treatment until the risk of suicide has passed.

"Suicidal ideation" is the term psychiatrists use to refer to suicidal thoughts. The response to "passive suicidal ideation" (those suicidal thoughts that are not driven by active intent nor accompanied by plans to act on them) is different than for people with "active suicidal ideation." In contrast to active suicidal ideation that requires an emergency response, passive suicidal ideation is not uncommon among people with HCV even when they are not on interferon-based therapy. Passive suicidal ideation requires careful monitoring and assessment for antidepressant medication, but does not necessarily require discontinuation of pegylated interferon treatment or psychiatric hospitalization.

One study found that 27% (15/55) of HCV-infected persons who were not on interferon-based treatment reported suicidal ideation compared to 43% (18/42) among those on treatment.[11] Individuals with passive suicidal ideation can benefit from increased support, clinical assessment, and management. However, passive suicidal ideation is often related to passing moments of sadness, or may reflect some instinctual effort to reestablish a sense of control at a time when illness and treatments can leave people feeling powerless and out of control.

Passive suicidal ideation is not related to an actual wish to die, and is not accompanied by a readiness to put thoughts into action. In fact, in the study mentioned above, 94% (17/18) of those HCV-infected individuals in the study who expressed suicidal ideation were able to complete a course of at least six months of interferon-based therapy. On the other hand, psychiatric evaluation should be considered if there is a question of active suicidal ideation.

If you find yourself having even passing thoughts of "ending it all" or "feeling better off dead," talk to your healthcare providers and ask to see a psychiatrist.

Psychosis on Interferon-Based Therapy

A study of 43 out of 943 patients who experienced psychiatric symptoms on standard interferon included four patients with a psychotic disorder (delusions and hallucinations).[61] There have also been a few case reports of individuals who experienced psychotic symptoms on standard interferon[62] and one series of four such patients.[63] While there have been few reports of psychotic symptoms on pegylated interferon, it is likely that some patients will also experience psychotic symptoms on pegylated interferon therapy as well.

The term "psychotic" refers to auditory hallucinations (hearing voices others don't hear), visual hallucinations (seeing things other people don't see), grandiose or paranoid delusions (extreme thoughts of fictional power or feelings that strangers on the street are talking about you or knowing your thoughts).

If you experience or have experienced any of these symptoms, be sure to let your healthcare providers know. You may be afraid or even ashamed to admit to your healthcare providers that you are experiencing these symptoms (or have previously experienced them while on or off drugs). Your fear may be because you have never experienced anything like this before and you don't want anyone to think you are "crazy." Or you may have had these experience before but are afraid because you have never told anyone about them before. You are not crazy, but you may be having side effects or symptoms that are very treatable. Remember, your healthcare providers can only help you with things they know you are experiencing.

Anxiety on Interferon-Based Therapy

Very few studies have focused on the symptoms of anxiety with inteferon-based therapy. The previously mentioned study found that 13 patients of the 43 patients who experienced psychiatric side effects on standard interferon therapy for HCV (total study involved 943 patients) were diagnosed with anxiety disorders.[61] Another found that 2 out of 60 patients required treatment for anxiety disorders while on standard interferon-based therapy.[64] While there are higher baseline rates of anxiety among patients with HCV prior to treatment[65], this seems to be a relatively uncommon side effect of standard interferon treatment, and is relatively unstudied with pegylated interferon.

Anxiety is more common among people with HCV before they start treatment. If you have experienced more severe anxiety than others on a chronic basis, or have ever been treated with psychiatric medications for anxiety or panic attacks, be sure to let your healthcare providers know. Together, you can consider restarting treatment for your anxiety before you begin your pegylated interferon plus ribavirin therapy.

Mood Changes Related to The Effects of Interferon-Based Therapy on Thyroid Function

Both hypothyroidism (low *thyroid* hormone levels) and hyperthyroidism (high thyroid hormone levels) have been associated with interferon-based therapy for HCV infection. Hypothyroidism is a well-known, reversible cause of depression that is associated with weight gain, decreased energy, sleepiness, and physical and mental slowness. Hypothyroidism often subsides once interferon treatment is completed. If the condition persists, it can be treated with thyroid hormonal supplements.

Severe hyperthyroidism (Grave's disease or destructive thyrotoxicosis), can cause symptoms that appear similar to mania with racing thoughts, physical agitation, excess energy, and rapid speech. If symptoms are severe and do not respond to medication to control the hyperthyroidism, interferon therapy may need to be discontinued.[65]

Prevention and Treatment of Psychiatric Side Effects of Interferon-Based Treatment

There are a number of important decisions you can make for yourself, even before you discuss whether to start pegylated interferon plus ribavirin treatment with your healthcare providers. If you start your treatment feeling in charge of yourself and with a commitment to complete therapy, you may feel more hope and pride as you complete each day of treatment - closer to reaping the full benefits of these powerful medications.

While there is no guarantee that any measure will prevent the occurrence of depression or other psychiatric side effects of interferon-based therapy, there are many things you can do to decrease the likelihood you will need to stop HCV treatment because of these side effects.

One of the most important things you can do is to be sure to seek treatment for preexisting psychiatric and substance use disorders, and to be sure that you are not in a state of depression before you start treatment for your HCV infection. Optimally, try to achieve a stable state of abstinence and sobriety — especially sobriety.

Stopping alcohol as soon as you can after you have been diagnosed with HCV is one of the most important steps you can take on behalf of your own health. If you drink alcohol before you start HCV treatment, you are in a sense, increasing the activity of HCV in your liver while thinking about starting a year-long treatment whose major goal is to decrease its activity. If there were a pill you could take that would eliminate the effects HCV on your liver that stopping all alcohol actually does, you would want to take it.

Seek out both formal treatment programs as well as 12-step programs such as Alcoholics Anonymous, Cocaine and Narcotics Anonymous. Consider taking disulfiram (Antabuse®) or acamprosate (Campral®), even in a monitored program

if that would give you more support in your goal of sobriety. Consider methadone or buprenorphine as substitution therapy for opiate addiction. Set up both formal and informal sponsors you can call when you need to talk with someone about impulses to relapse.

Consolidate your natural support networks by letting others who are close to you know what you are going through. Make your healthcare providers feel part of "your team" by talking with them and establishing a relationship of trust and collaboration.

And do all those things you already know are good for you - and that your primary care providers have been telling you - such as paying attention to healthy nutrition, good sleep hygiene with regular hours, and some exercise. There is never a better time to start to pay more attention to these than now.

Preventive (Prophylactic) Antidepressant Medication

In addition to treating a current major depressive disorder, some people have recommended that antidepressant medications be started before interferon-based therapy begins in people who have a prior history of major depressive episodes. One trial using citalopram (Celexa®) pretreatment in patients on pegylated interferon plus ribavirin with a psychiatric history found lower rates of depression in pretreated patients than in those who did not receive citalopram.[67]

However, another study already discussed[11] indicated that only half of those with a prior history of psychiatric disorder at baseline required antidepressant treatment during pegylated interferon plus ribavirin treatment. Preventive (prophylactic) use of antidepressant medications would be exposing half of the treatment population to medications (and their side effects) that they didn't actually need.

If you have had a course of antidepressant medication and then relapsed with depression and required another course of antidepressants, you are at higher risk of relapse during interferon-based therapy. You should consider discussing going back on antidepressant medication with your psychiatrist before beginning interferon-based therapy. Or you may feel, as many people do, that you are already taking enough medication and because pegylated interferon plus ribavirin induced depression usually responds well to treatment, you may choose to wait and see how you feel during the treatment. This is likely a workable solution as long as you are closely monitoring for depressive symptoms, or are seeing a psychiatrist regularly during your HCV treatment.

Antidepressant and Mood Stabilizing Medication

If you experience a major depressive disorder during pegylated interferon plus ribavirin treatment, almost all antidepressants have been reported to be effective and tolerated as treatment. The choice of one antidepressant over the other is usually based on their side effect profile, as it routinely is for non-HCV patients.

One study specifically assessed citalopram (Celexa®) in the treatment of depression among patients with chronic hepatitis C. It was found that in patients with liver enzymes less than 2.5 times above the normal range, citalopram blood levels were not significantly different in depressed patients with and without liver disease[67] and that it was an effective, well-tolerated antidepressant.

There are many case reports of antidepressants that have been successfully used in the treatment of major depressive disorders during interferon-based therapy. These are extensively reviewed in papers[57, 68] that also discuss side effects, drug-drug interactions (such as the caution regarding bleeding problems when using the combination of interferon, non-steroidal anti-inflammatory agents and selective serotonin reuptake inhibitor [SSRI] antidepressants), metabolism, dose and duration of treatment, and choice of agent that are beyond the scope of this chapter.

Antidepressant agents showing efficacy and tolerability for HCV patients on interferon-based therapies are shown in Table 1.

Table 1. Antidepressant Medications Showing Efficacy and Tolerability for HCV Patients on Interferon-Based Therapy

Drug Class	Specific Medications
selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa®) fluoxetine (Prozac®) paroxetine (Paxil®) sertraline (Zoloft®)
noradrenergic/serotonergic antidepressants	duloxetine (Cymbalta®) mirtazapine (Remeron®) venlafaxine (Effexor®)
noradrenergic/dopaminergic agents	buproprion (Wellbutrin®)

These papers also discuss the possible role of psychostimulants such as methylphenidate (Ritalin®) or modafinil (Provigil®) for interferon-induced fatigue.

Similarly, most mood stabilizing agents have been reported to be safe and effective in the treatment of bipolar disorders among patients with HCV and those on interferon-based therapy. Valproic acid (Depakote®), of particular concern because of an occasional association with elevated liver enzymes, was not shown to elevate liver enzymes more in patients with chronic hepatitis C than other psychiatric medications, specifically antidepressants, lithium, and gabapentin.[69] However, many doctors are still cautious about the use of valproic acid in patients with HCV and significantly elevated liver enzymes. Often other medications are substituted instead of using valproic acid to control psychiatric symptoms in such situations. Another study[70] reviews a number of competing concerns with mood stabilizers such as the lithium and carbamazepine (Tegretol®). Olanzapine (Zyprexa®) has been used safely to help with mood stabilization in chronic hepatitis C patients with bipolar disorder.

There are also many antianxiety agents such as lorazepam (Ativan®), and medications to help you sleep such as trazadone (Desyrel®) or zolpidem (Ambien®) that have been used by people with HCV safely and with good result.

The biggest barrier to getting treatment for depression and bipolar mood disorders is likely to be not recognizing their symptoms early and not acknowledging these symptoms need treatment. In general, there are as many psychiatric medications available to people with HCV (with a few exceptions that your healthcare provider will know about) as there are to the general population.

Summary

Combination therapy with pegylated interferon plus ribavirin has significantly improved response rates across all genotypes compared to standard interferon. But this therapy is still associated with depression and physical side effects that can negatively affect quality of life.

Depression and other mood disorders are effectively treated with standard antidepressant and mood stabilizing medications. If you have a prior history of psychiatric, alcohol or substance use disorders, you should consider getting psychiatric and/or substance treatment for stabilization before starting pegylated interferon plus ribavirin treatment.

On the other hand, patients with psychiatric and substance used disorders should not automatically be considered ineligible for pegylated interferon plus ribavirin treatment. Similarly, psychiatric disorders induced by pegylated interferon plus ribavirin treatment should be treated directly and not by reduction of dosage or early discontinuation of HCV treatment unless necessary.

You are likely feel better about yourself and your treatment if you learn as much as you can about them, and continue to discuss your experiences and concerns with your healthcare providers and your support system. Despite a potentially challenging course of treatment over 6 to 12 months, many people with HCV completely clear the virus and achieve a sustained virologic response with normalization of their mood and resolution of physical side effects as soon as they complete their treatment.

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