

# Interferon and Risk for Drug-Seeking Behavior

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## Abstract

Interferon (IFN), a biological medication used to treat viral hepatitis and certain cancers, has clinically significant potential to cause a wide range of adverse neuropsychiatric effects. The spectrum ranges from agitation, aggression, insomnia and irritability, to suicidal thought and drug-seeking behavior (DSB). Out of a total population of 353 patients infected with hepatitis C virus (HCV), 132 patients at an inner city hepatitis clinic underwent treatment. Those treated were questioned at intake and on a regular basis for the initiation or increase of DSB. In addition, when warranted, patients were tested for the presence of drugs they were not prescribed. Over a four year period, ten patients (4 currently receiving treatment with IFN, 4 with prior treatment, and 2 who never received IFN) reported an increase in DSB. The danger of developing IFN-induced DSB appears to be relatively low (< 3%) in our patient population, and we also observed DSB in HCV patients who were not treated with IFN. To our knowledge, this is the first study of the incidence of DSB associated with IFN treatment for HCV that completely surveyed the HCV-treated population and used urine toxicology to verify illicit drug use.

## INTRODUCTION

Patients with DSB have an inappropriate focus on obtaining a desired abused drug, i.e. cocaine, opioids, methamphetamine, etc. without concern of other more appropriate issues, such as diagnosis or treatment of their addictive behavior (Vissers, 2002). DSB includes abused drug preoccupation (talk and memories), and the craving and actual search for and use of abused drugs. It may be true that DSB as an observed action may not always be preceded by drug-related thoughts and memories as associated cognitive activity. However, it is likely that in most cases these cognitive activities precede DSB as action. Since DSB and use has the potential for dire consequences to IFN therapy in the treatment of HCV, we have questioned for the self-report of such drug abuse-related cognitive activity in regular office visits.

As a general rule, it is reasonable to urge patients to avoid any stimulus to DSB while undergoing treatment for viral hepatitis, because of the potentially harmful effects of non-prescribed and addictive medication on antiviral therapy. Since the principle routes of contraction of infection for HCV include injection drug use (IDU), any increase in DSB caused by a side effect of a therapeutic (such as IFN) could become counter-therapeutic. IDU is known to suppress the immune system in some [for example, HIV] viral infections (Thompson & Salvato, 1998). Even though frequent illicit

drug use during treatment of HCV may lead to decreased adherence (Sylvestre & Clements, 2007), several researchers (Robaey & Buntinx, 2005); (Sylvestre, Litwin, Clements, & Gourevitch, 2005); (Sylvestre & Clements, 2007); (Grebely et al., 2007) have reported that illicit drug use itself may not counter the therapeutic response to IFN.

Although the Warnings Section, Neuropsychiatric Subsection of the prescribing information (PI) for pegylated interferon alpha 2 (IFN) mentions that "relapse of drug addiction" may occur in patients, no specific information is given on the frequency of occurrence, the causal relatedness or predisposing or inciting factors. Upon query to the manufacturers, they were not able to supply specific data in these areas. A search of Medline also did not reveal specific published information in this regard. The aim of this observational study was to determine the incidence of DSB in a population being treated for HCV in an inner city community hospital, using standardized and previously validated approaches.

## METHODOLOGY

Three hundred fifty three patients with HCV were evaluated for treatment at the Hepatitis Clinic of Cooper Green Mercy Hospital (CGMH), an inner city safety net medical facility in Birmingham, Alabama. Patients did not automatically receive antidepressants as a prophylactic action prior to

therapy with IFN and weight-based ribavirin (RBV). Treatment for HCV used standard protocols (NIH Consensus Statement).

Patients were offered treatment for HCV if they met the following three criteria: 1) viral load > 400,000, 2) symptomatic for HCV (for example chronic fatigue, weakness, abdominal pain, nausea), and 3) elevated liver enzymes (AST > 2 times upper limit of normal). Patients not meeting these criteria could still be considered for an individual treatment decision, if after an explanation of why they were not optimal candidates for treatment they still desired this option. Patients were not offered treatment for HCV if they continued to consume more than occasional alcohol, were using or had used within the last 3 months cocaine, methamphetamine or heroin or non-prescribed Schedule II medications, verified by random urine screens, met any of the exclusion criteria cited by the manufacturer, or declined treatment. Methadone use within the confines of a maintenance program was allowed.

Patients received either pegylated interferon alpha 2a (Pegasys, Roche, 180ug) or 2b (Peg-Intron, Schering, weight based) once per week, each with weight-based ribavirin (WBR) twice a day (unless contraindicated). Before initiation of treatment, all patients underwent extensive classroom education on their disease, treatments, alternatives, expected outcomes, and potential adverse effects. In addition, patients were cautioned of the need to avoid alcohol and illicit drugs during treatment with IFN, particularly cocaine, heroin, and (meth)amphetamines. Patients were seen routinely at 2, 4, 6, 8 weeks of treatment and monthly thereafter, unless their medical condition required more frequent visits. At visits, patients were questioned about the presence of anxiety, depression, insomnia, agitation, suicidal thoughts, DSB (previously defined), and other psychiatric symptoms, as defined in DSM IV. A subjective assessment of the onset of mood disorders was made at each visit. If the patient stated that they experienced new DSB or increased DSB, a detailed drug history was taken, and a urine drug screen was collected.

A nine panel urine toxicology panel was assayed for using a Beckman Coulter multichannel chemistry analyzer. The following drugs were part of the assay: amphetamine, barbiturates, benzodiazepine, cocaine, methadone, methamphetamine, opioid screen at two levels of sensitivity, and THC. The opioid screens indicated that an opioid was present, but did not specify which opioid was involved. The

collection of urine samples was not witnessed.

Baseline questioning was designed to capture information potentially relevant to increased susceptibility to DSB : 1) basic patient demographics (date of birth, sex), 2) past medical history (hypertension, diabetes, heart disease, smoking, alcohol), 3) past IV drug use, 4) use of cocaine), heroin, marijuana, alcohol or tobacco dependency, 5) attendance in AA and or NA groups, 6) family history of substance abuse or psychiatric illness, and 7) prior psychiatric problems (depression, agitation, anxiety, suicidal thought and others). Identifiable risk factors for increased DSB were defined, for purposes of this protocol as a positive response to any of #3-7 (Dieperink, Ho, Thuras, & Willenbring, 2003); (Edlin et al., 2001); (Fried, 2002).

We entered into our database the patient demographics, viral load at start, during and after treatment, decision to treat, risk factors for drug response, urine drug screens, adverse effects and other data for all patients with viral hepatitis seen in the hepatitis clinic at CGMH for the four year period 2004-2007. A directed search of the data for DSB was prepared; no change in therapeutic decision was based upon the collection of this data. The hospital Institutional Review Board approved the use of anonymous demographic and incidence data collection for the purpose of preparing this publication.

Before antiviral treatment was offered, all patients were provided with a discussion, brochures and videos of HCV infection, treatment options, an understanding of the potential adverse effects of medicine including DSB, alternatives to treatment, and required to attend a class for the lay person covering all aspects of HCV disease and treatment. A statistical data analysis was not performed in this preliminary and epidemiologic study.

## **RESULTS**

The demographics of the population at the Hepatitis Clinic, evaluated and treated at CGMH is summarized in Table 1. Patients with a background of IDU and former non-IDU were more likely to be in the population that met screening criteria for active treatment.

**Figure 1**

Table 1: Demographics of Patient Population

	Overall HCV patients	Treated for Hep C
Total	353	132
Average age	51 years	50 years
Males	57%	54%
African American	55%	52%
Former IDU* (when known)	25%	35%
Former non-IDU*		
Currently drinking alcohol **		

\* when known

\*\* described as more than rarely, and includes self-descriptions such as active, weekends, social

The principle psychiatric problems patients at our clinic experienced were anxiety, insomnia and depression. These psychiatric problems may have been causally related to IFN use, using standard accepted definitions of pharmaceutical specific causation (Marks, 2005), were not unexpected and were warned of in the Prescribing Information (PI).

Increases in depression and anxiety due to IFN were recently reviewed elsewhere (Marks, Adineh, Wang, & al, 2007).

**Figure 2**

Table 2: Increased Drug Seeking Behavior During Study Period

Patient ID#	48	69	379	372	3	18	30	192	383	278
Rx IFN	IFN- $\alpha$ 2a	IFN- $\alpha$ 2b	IFN- $\alpha$ 2b	IFN- $\alpha$ 2b	IFN $\alpha$ 2a AE, D/C	Prior IFN- $\alpha$ 2a	Prior Peg-IFN	Prior Rx	None	None
Age	46	37	50	50	45	49	54	57	51	49
Sex	M	M	M	M	M	F	M	M	F	F
New drug use	None, but DSB for methadone	Cocaine	Non-Rx methadone	RPCU	Cocaine prior to IFN Rx	RPCU	RPCU	RPCU	Cocaine	Cocaine
CNS adverse effect	Suicidal and homicidal ideation		None							
Methadone	Not taking at time of AE	Not taking at time of AE	Non-Rx methadone	None	None	Yes	MMT	None	None	None
IV drug use	Prior	None	No	Prior	Prior	Prior	Prior	Prior		Prior
Alcohol	Recent	None in 10 yrs	2 yrs previous	Occ	Prior	No	Current	Prior		Current
Action taken	D/C IFN, resolved		D/C IFN as NR			Refer to rehab		Rehab		

RPCU: Resumption of prior cocaine use IDU: IV drug use

IFN: interferon  $\alpha$ 2

D/C: discontinued

MMT: methadone maintenance treatment AE: adverse effect

Four patients (#48, 69, 379, 372) treated with IFN, four patients (#3, 18, 30, 192) previously treated with IFN and two patients (#383, 278) who were never treated with IFN reported increased DSB during this study period (Table 2). This gave the overall incidence of DSB during INF treatment to 3% (4/ 132), and <1% (2/262) in HCV patients who were not treated. Three patients (18, 192, 30) previously treated with IFN resumed cocaine use. One patient (#3) had prior treatment with IFN and prior cocaine use, which was not resumed during the study period.

In addition to having a higher incidence of past IDVU, it was not uncommon for patients in our clinic to receive MMT (Table 3). Almost all patients who received MMT did so for pain control, as opposed to treatment of drug dependency.

**Figure 3**

Table 3: Methadone use and DSB in MMT Patients Treated For HCV.

HCV Treatment Status	Total	Receiving methadone	DSB on Methadone
Responder, completed	15	7	#18 RPU after IFN
Responder, in treatment	4	2	#353 amphetamine methamphetamine
Started treatment		2	
Non-responder	9	2	
No need to treat	13	3	
Not candidate for treatment	36	6	

Legend: The occurrence of DSB in our patient population with respect to known use of methadone, and to antiviral response category.

Seven patients (Table 3) receiving MMT (for pain control, rather than drug dependency) responded to treatment, four were not yet ready for response determination, and two MMT patients were nonresponders to IFN. Overall, regardless of MMT, three of five responders who tested positive for cocaine did so during treatment with IFN and none of the four nonresponders who tested positive for cocaine did so during treatment.

During the study period, 213 patients were checked by urine drug screen (UDS), including all 132 patients who were treated with IFN and all patients receiving MMT (Table 4). Two (#18, 30) patients currently on MMT admitted to resumption of cocaine use, although this occurred one year after treatment with IFN had already ended. Both patients stated that the prior use of IFN did not increase their DSB and had no role in resumption of use of cocaine.

**Figure 4**

Table 4: Urine Drug Testing for Cocaine during Study Period for IFN-Treated v Untreated HCV Patients

	Total UDS	UDS during treatment with IFN	UDS+ outside of IFN treatment period	UDS+ during IFN treatment period
Untreated patients	81	0	16+ cocaine	NA
Treated with IFN+RBV	132	38	8+ cocaine	3 cocaine

Testing for illicit drug use, particularly cocaine, at the clinic. Eleven of the patients who were treated with IFN tested positive for cocaine, three of these eleven tested positive

while being treated with IFN.

## DISCUSSION

Our data indicate that the danger of developing IFN-induced DSB appears to be relatively low (3%) in both treated and previously treated HCV patients, and <1% (2/262) in untreated HCV patients. This is reassuring information for those engaged in the primary care of patients with hepatitis, since in addition to DSB, use of IFN can be associated with apathy, depression, fatigue, irritability, cognitive dysfunction and suicidal thoughts (PI).

To our knowledge, only Sylvestre (Sylvestre, Litwin, Clements, & Gourevitch, 2005) have reported empirical data on the incidence of resumed drug abuse or other DSB while on IFN. While Sylvestre (Sylvestre, Litwin, Clements, & Gourevitch, 2005) and others have reported that intercurrent drug abuse (heroin, methamphetamine, cocaine) did not correlate with a decreased antiviral response, these authors did not comment on the issue of whether treatment of HCV can induce DSB. Our data may be the first concerning the incidence of DSB associated with IFN treatment for HCV that completely surveyed the HCV-treated population and used abused drug urine toxicology to verify illicit drug use.

Our data indicate that in this patient population, as in the general population of (former) drug users, the use or the resumption of use of illicit drugs, such as cocaine, can occur regardless of exposure to IFN. It also calls into question the reliability of statements of patients that their use of IFN led to DSB, although one might conclude that they certainly should be the best qualified to make this determination. Results in our patient population are, therefore, consistent with the findings of other researchers studying different populations of patients, and suggest that cocaine use may not interfere with the anti-HCV response to IFN. IFN does not seem to cause a heightened DSB, and the incidence of IFN-induced DSB does not seem to be more than 3%.

There are several reasons why some patients in our treatment population experienced DSB. First, patients who are receiving MMT may develop DSB because some of the flu-like side effects of IFN (for example, nausea, vomiting, headache, abdominal pain) may mimic opioid withdrawal symptoms (Matthews, Fireman, Zucker, Sobel, & Hauser, 2006). For physicians treating HCV patients at risk for IDU, this can be a significant concern. Second, craving may also be secondary to mood changes (for example depression) caused by antiviral therapy (IFN) or could be cue-related to the needles that are used to deliver IFN. Sixteen percent of

our HCV population had used IV drugs within the last 7 years. Thirdly, at least one patient in our patient population stated that he had resumed cocaine use during treatment with IFN in order to treat generalized pain experienced as a result of IFN treatment.

Sylvestre (Sylvestre, Litwin, Clements, & Gourevitch, 2005) (personal communication) recently conducted a multicenter study on treatment of 67 HCV patients receiving MMT for opioid dependency. During treatment, 20% of the patients continued to consume ethanol, 36% used hard drugs, 61% used any illicit drug, and 45% increased their methadone dose by a median of 15 mg. The overall impact of barriers of continued illicit drug use on virologic outcomes showed that more patients who were on MMT dropped out of treatment. These investigators observed that intercurrent drug use did not lead to a reduction in HCV outcomes, data which are consistent with other researchers (Sylvestre & Clements, 2007 ); (Grebely et al., 2007 ). Sobriety length did not seem to correlate well with adherence to therapy, but regular (vs no) drug use correlated highly to therapy program adherence. Marijuana use also correlated well to adherence to the treatment protocol, but the presence of psychiatric disorders did not. Nine patients on MMT (16%) experienced treatment (IFN)-related drug craving, and 3 of 57 (5%) patients reported that IFN contributed to a relapse in drug use. These findings are consistent to our own. Fifteen patients in the Sylvestre study (Sylvestre & Clements, 2007 ) (26%) indicated that HCV treatment contributed to drug use, and 4 of 57 (7%) said HCV treatment contributed to hard drug use. In 2 of these patients (4%), the drug use became regular. These data are important because they point to IFN-induced DSB, at least in that patient population. The numbers reported herein for DSB are much lower, but our population is also very different. IDU may also impact adherence to treatment (Sylvestre & Clements, 2007 ).

In our patient population, few simultaneously received MMT, and those that were took MMT almost exclusively for pain management as opposed to addiction treatment. None of the four patients (#48, 69, 379, 372) who reported DSB during treatment with IFN was simultaneously taking MMT. Eleven of the patients who were treated with IFN tested positive for cocaine, and four of these eleven ((#18, 30, 192, 353) tested positive while being treated with IFN. Although none of the patients in our clinic who were taking MMT for analgesia reported an increase in DSB while on treatment with IFN, four (#18, 353, 30, 192) tested positive for drug use during treatment with IFN.

The ability of medication to stimulate drug-craving is not unique to IFN. In patients who abuse both amphetamine and cocaine, haloperidol and thioridazine given therapeutically may increase drug cravings (Colpaert, Niemegeers, & Janssen, 1978 ); (Brown, Nejtek, Perantie, Rajan Thomas, & Rush, 2003 ). Other than avoiding use of IFN in individuals with significant drug abuse history and significant baseline DSB, there is currently no way to predict whether an individual will respond to IFN with negative neuropsychiatric effects. Several risk factors are thought to increase the probability of emergent psychiatric comorbidity during IFN- $\alpha$  treatment, and were noted in patient intake (see end of Methods Section). It is possible that patients being treated for HCV who are at risk of an increase in DSB, as determined by a screening evaluation, will show corresponding increased brain activity through functional neuroimaging in those areas previously associated with drug craving (Magalhaes, 2005); (Garavan et al., 2000); (Sinha & Li, 2007 ); (Paulus, Tapert, & Schuckit, 2005 ).

Because patients were interviewed by the treating physician (DHM) to collect self report data on DSB, rather than by someone not involved in treatment of HCV, the DSB may be under-reported, and an ascertainment bias could be present. The incidence data should be considered conservative and in need of further study using urine toxicology verification methods. Urine toxicology testing for abused drugs was not routinely utilized throughout active treatment and thus some drug use could have occurred but went unreported to the treating physician. We intend in follow-up studies to correct for this by more regular screening.

The incidence of DSB we have detected is much lower than the incidence of IDU (63-89%) reported by others (Thomas et al., 1995 ); (Des Jarlais et al., 2005 ) in patients with HCV. Of course, DSB in our patient population detects the use of non-prescribed medications; our patients are not primarily drug users. Our patients who are on MMT take it for pain control, not ablation of drug craving.

Some investigators (Robaey & Buntinx, 2005); (Sylvestre, Litwin, Clements, & Gourevitch, 2005) hold that the presence of IVDU DSB (injection heroin abuse in patients on MMT) in an HCV patient before treatment with IFN, or the development or increase in DSB during IFN treatment may not preclude use of IFN in those patients. In fact, the therapeutic response to HCV by IFN has been reported as similar in patients who were and who were not abusing illicit (heroin) substances (Robaey & Buntinx, 2005); (Sylvestre, Litwin, Clements, & Gourevitch, 2005), and we have not

noted evidence to the contrary.

In conclusion, HCV patients receiving IFN are at risk for DSB, although the frequency may be less than previously thought. In part, this is undoubtedly related to the milieu surrounding illicit drug use. Even without that component, IFN can induce DSB, and it is this ability, with or without the concurrent use of illicit drugs, that we hope to better identify with follow-up studies.

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