Perspectives on Hepatitis C Infection

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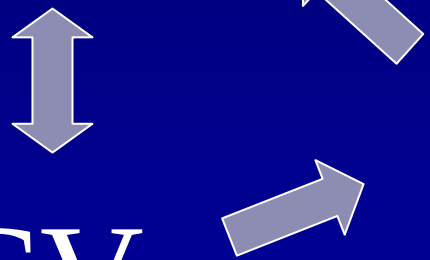
Mental Illness

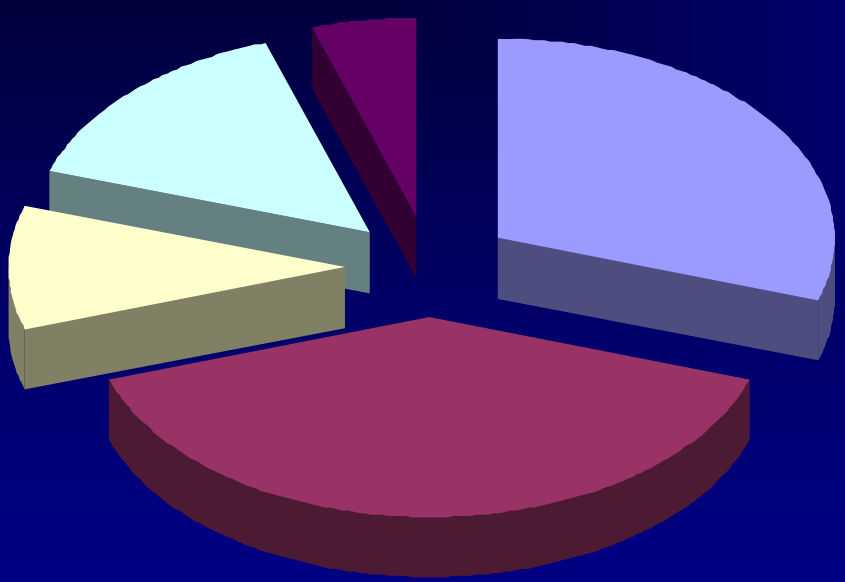
Demoralization
Substance Use
Depression



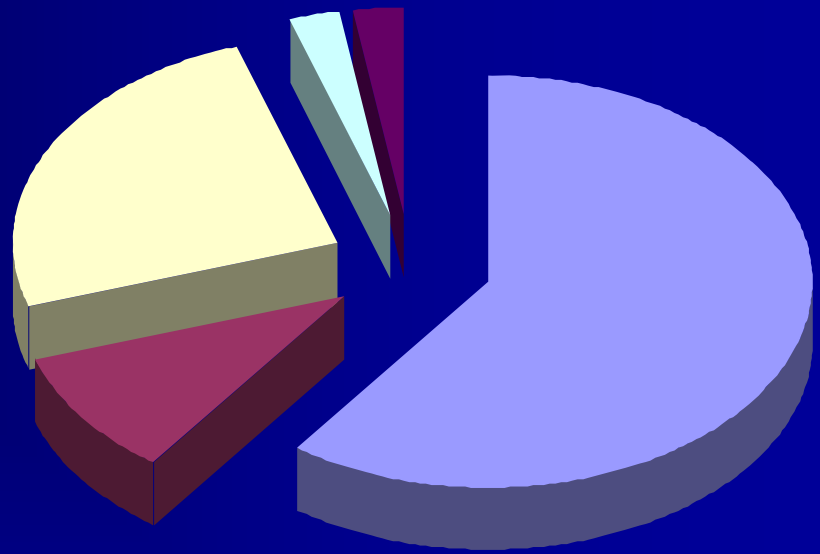
IFN

HCV

Hepatitis C - Epidemiology



Before 1985

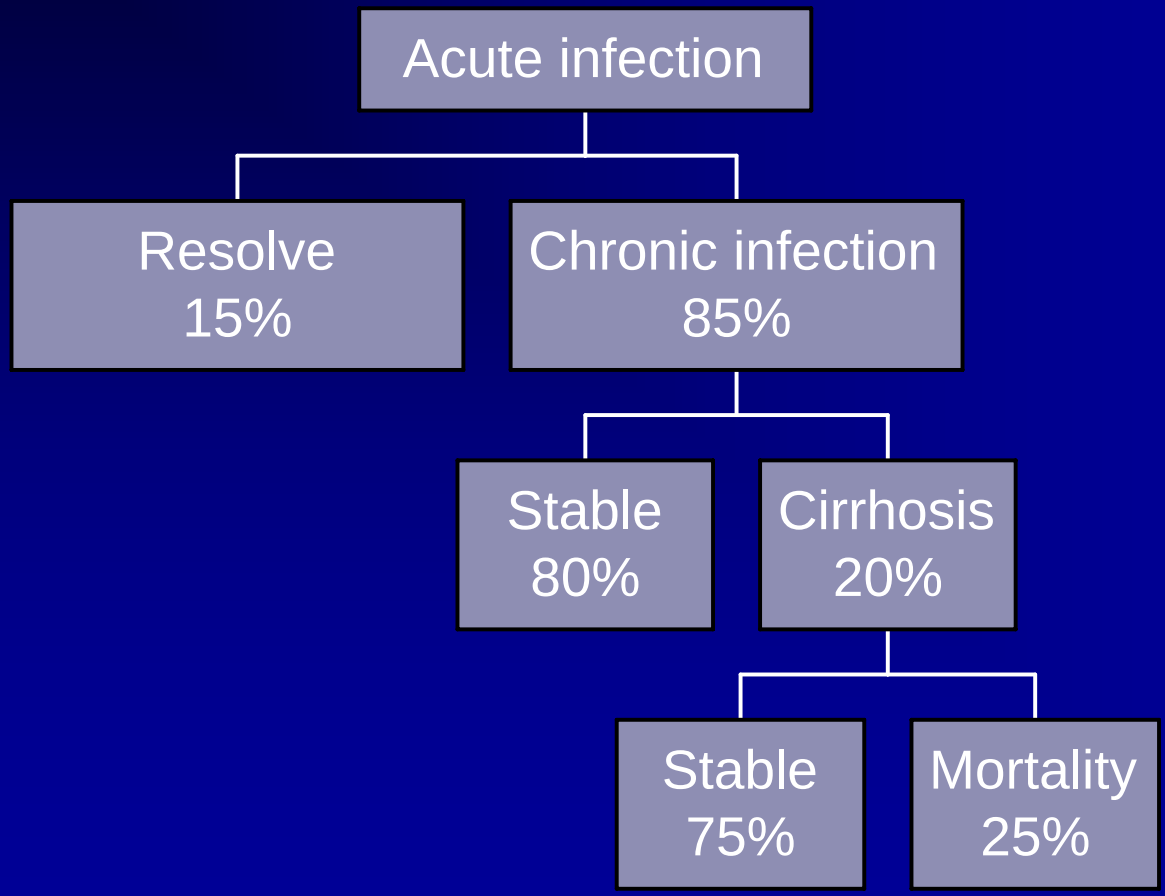


1999

Illegal Drug Use
Transfusion
Sexual
Other
Unknown

Adapted from Williams I, Am J Med, 1999.

Hepatitis C Infection - Natural History



Seeff LB, Am J Med, 1999

Chronic Hepatitis C - Factors Promoting Progression or Severity

- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- ?Other
  - Male gender
  - Other co-infections (e.g., HBV)

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

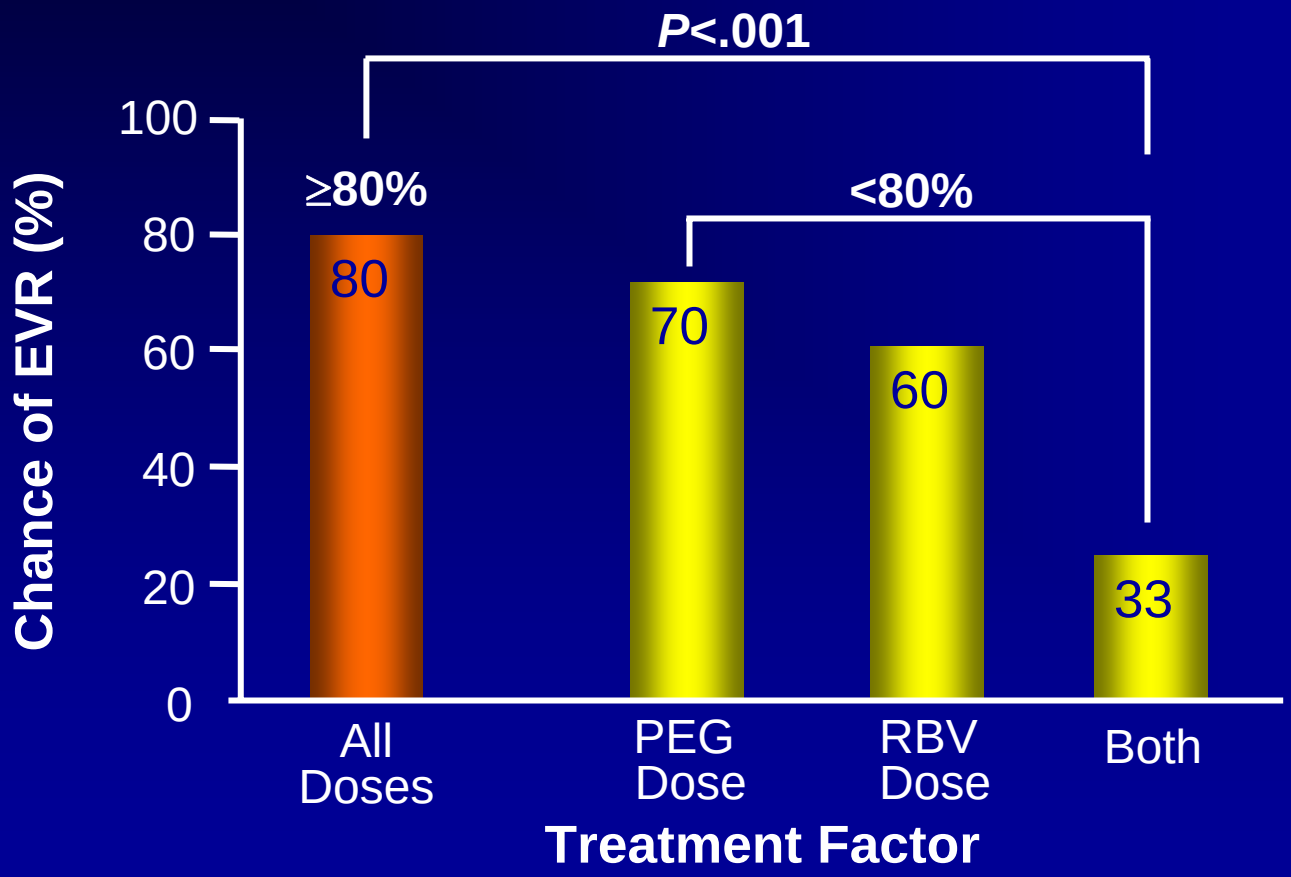
Key Points of PEG IFN/RBV Trials

Cumulative Genotype Data

- Mean probability of SVR with GT 1
  - 42%-47%
- Mean probability of SVR with GT 2,3
  - 76%-84%

Fried et al. *N Engl J Med*. 2002;347:975-982.
Hadziyannis et al. *Ann Int Med.* 2004;140:346-357.
Manns et al. *Lancet.* 2001;358:958-965.

Adherence During First 12 Weeks of Therapy Effects EVR
PEG IFN alfa-2b/RBV



Davis et al. *Hepatology*. 2003;38:645-652.

HCV and Depression

- Statistically higher BDI scores in HCV patients compared with other liver diseases
- Mildly elevated Zung scores on all 96 HCV+ patients prior to IFN treatment
- 45.3% of HCV+ patients screened positive for depression on HADS vs. 4% of healthy controls

Singh et al, 1997
Malaguarnera et al, 1998
Goulding et al, 2001

HCV and Depression

- Found major depression or dysthymia in 30% of patients prior to IFN therapy
- Depressive symptoms reported in 57.2% of HCV+ active drug users
- SCID on 50 patients prior to IFN 7/50 (14%) with previous major depression

Yates et al, 1998
Johnson et al, 1998
Pariante et al, 1999

HCV and Depression
Patients Receiving IFN and RBV

Davis et al (1998)	Depression in 16% of IFN/RBV treated patients No significant difference from IFN monotherapy
McHutchison et al (1998)	Treated patients • Depression in 36% • Irritability in 32% • Anxiety in 18%

IFN, interferon.

Davis et al. *N Engl J Med*. 1998;339:1493-1499.
McHutchison et al. *N Engl J Med*. 1998;339:1485-1492.

PEG IFN/RBV-related Depression
Patients Receiving PEG IFN and RBV

Manns et al (2001)	HCV-infected patients: PEG IFN alfa-2b 1.5 µg/kg + 800 mg RBV Depression—31% Irritability—35%
Fried et al (2002)	HCV-infected patients: PEG IFN alfa-2a 180 µg + 1000-1200 mg RBV Depression—22% Irritability—24%

PEG IFN, pegylated interferon; RBV, ribavirin.

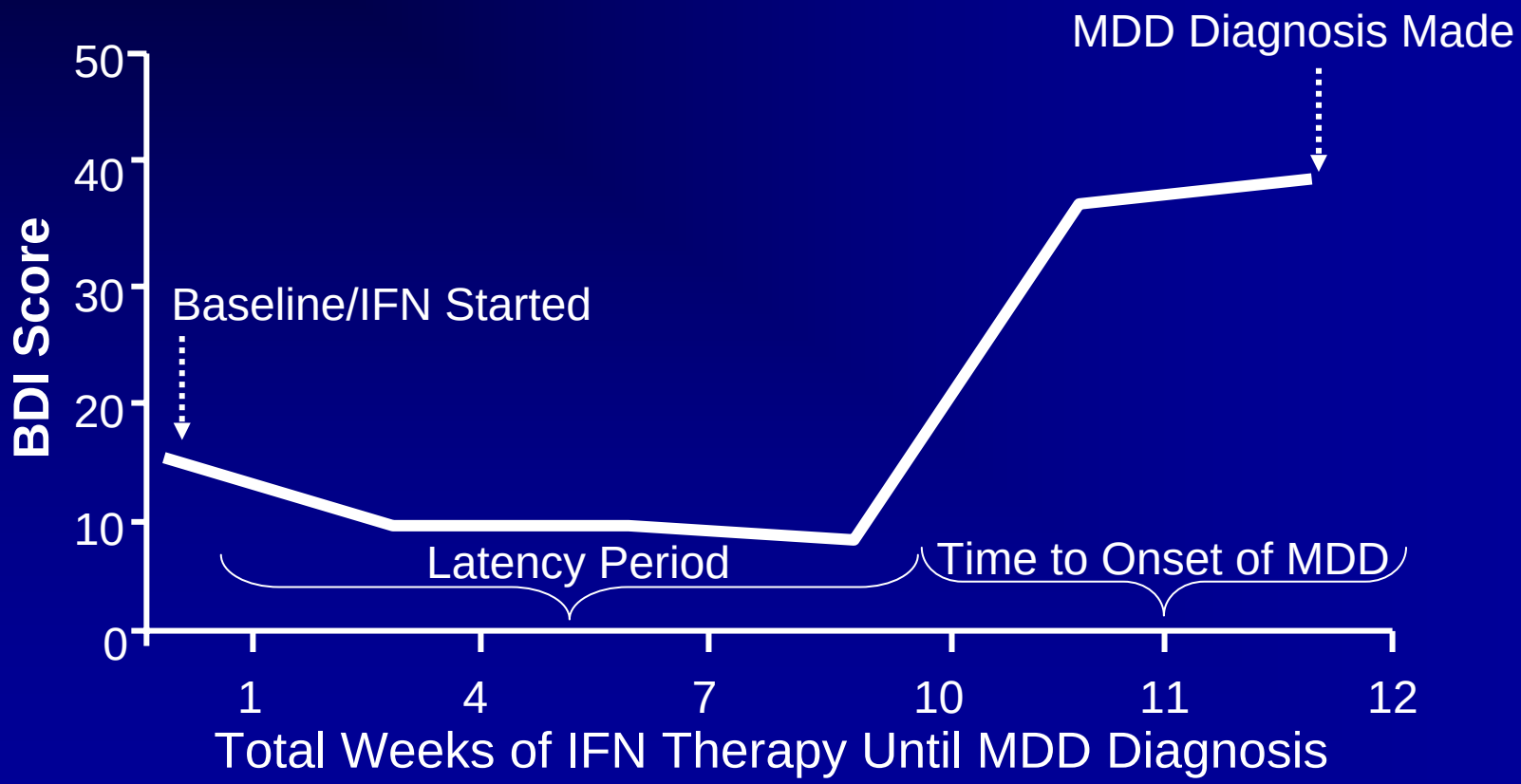
Fried et al. *N Engl J Med*. 2002;347:975-982.
Manns et al. *Lancet.* 2001;358:958-965.

PEG IFN/RBV-related Depression
New Findings

Raison et al (2003)	Subset analysis of patients receiving PEG IFN alfa-2b/standard vs wt-based RBV Direct relationship between depression and RBV dose
Raison et al (2003)	Subset analysis of patients receiving PEG IFN alfa-2b/standard vs wt-based RBV Direct correlation between depressive symptoms and failure to clear virus (independent of other variables)

Raison et al. *Hepatology.* 2003;38(suppl 1):326A.
Raison et al. *Hepatology.* 2003;38(suppl 1):325A.

Rapid Escalation of IFN-Induced Depressive Symptoms: *Threshold Effect*



IFN, interferon; MDD, major depressive disorder.

Hauser et al. *Mol Psychiatry.* 2002;7:942-947.

N=39

Treatment of Major Depression in Patients with HCV Infection

- Gleason et al, 2002
  - Enrolled 15 HCV-infected patients not currently receiving IFN
  - 4 patients initiated IFN during study
  - 13/15 responded* to an open trial of citalopram at 8 week follow-up

*≥50% reduction in HAM-D score

Goals of Depression Treatment for IFN-treated Patients

- Alleviation of symptoms
- Adherence to dose and duration of IFN therapy

Treatment of Depression Induced by IFN/RBV

Author (N)	Study Type	Outcome
Levenson et al, 1993 (N = 1)	Case report (CR), open label trial (OLT)	Response to fluoxetine
Goldman, 1994 (N = 1)	CR, OLT	Response to nortriptyline
Gleason et al, 1999 (N = 5)	Case series (CS), OLT	Response – sertraline, paroxetine, imipramine Failure – sertraline X 2, paroxetine

CR, case report; CS, case study; OLT, open-label trial.

Gleason, Yates. *Psychosomatics.* 1999;40:510-512.
Goldman. *Psychosomatics.* 1994;35:412-413.
Levenson, Fallon. *Am J Gastroenterol.* 1993;88:760-761

Treatment of Depression Induced by IFN/RBV

Author (N)	Study Type	Outcome
Schramm et al, 2000 (N = 10)	CS, OLT	Response–sertraline x 10
Gleason et al, 2002 (N = 4)	OLT	Response–citalopram x 4
Hauser et al, 2002 (N = 13)	Prospective, OLT	Response–citalopram x 9, fluoxetine, bupropion Failure–citalopram x 3

CR, case report; CS, case study; OLT, open-label trial.

Gleason, Yates. *Psychosomatics.* 1999;40:510-512.
Hauser et al. *Mol Psychiatry.* 2002;7:942-947.
Schramm et al. *Med J Aust.* 2000;173:359-361.

Treatment of IFN-Induced Depression in HCV

Overall success rate of treating depression induced by IFN is 29/35 patients (83%)

	Fluox	Sert	Parox	Cital	Buprop	NTP	IMI
Success	2	11	1	13	1	1	1
Failure	0	2	1	2	0	0	0
Rate	100%	85%	50%	87%	100%	100%	100%

Gleason, Yates. *Psychosomatics.* 1999;40:510-512.
Goldman. *Psychosomatics.* 1994;35:412-413.
Hauser et al. *Molecular Psychiatry.* 2002;7:942-947.
Levenson, Fallon. *Am J Gastroenterol.* 1993;88:760-761.
Schramm et al. *Med J Aust.* 2000;173:359-361.

Prophylaxis for IFN-Induced Depression in Malignant Melanoma

Hauser et al (2000)	Fluoxetine: successful prophylaxis with 1 patient who had 2 prior depression-related IFN discontinuations
Musselman et al (2001)	Paroxetine: double-blind, placebo-controlled trial (average = 31 mg/d) in 40 patients Paroxetine group: statistically significant ↓ rate of depression and ↓ likelihood of IFN discontinuation

IFN, interferon.

Hauser et al. *Psychosomatics*. 2000;41:439-441.
Musselman et al. *N Engl J Med*. 2001;344:961-966.

Prophylactic Citalopram
PEG IFN/RBV-related Depression

		History	Prophylactic antidepressant	On-therapy antidepressant	Depression rate
(n = 11)	A	Psych history (-)	None	None	64%
(n = 11)	B	Receiving methadone substitution	None	None	55%
(n = 14)	C	Receiving methadone substitution	Citalopram 20 mg QD initiated	Citalopram 20 mg QD continued	14%

***P* = .028**

2 weeks prior to PEG IFN/RBV

PEG IFN/RBV initiated

PEG IFN/RBV Tx Month 4

Schaefer et al. AASLD; October 24-28, 2003; Boston, Mass.

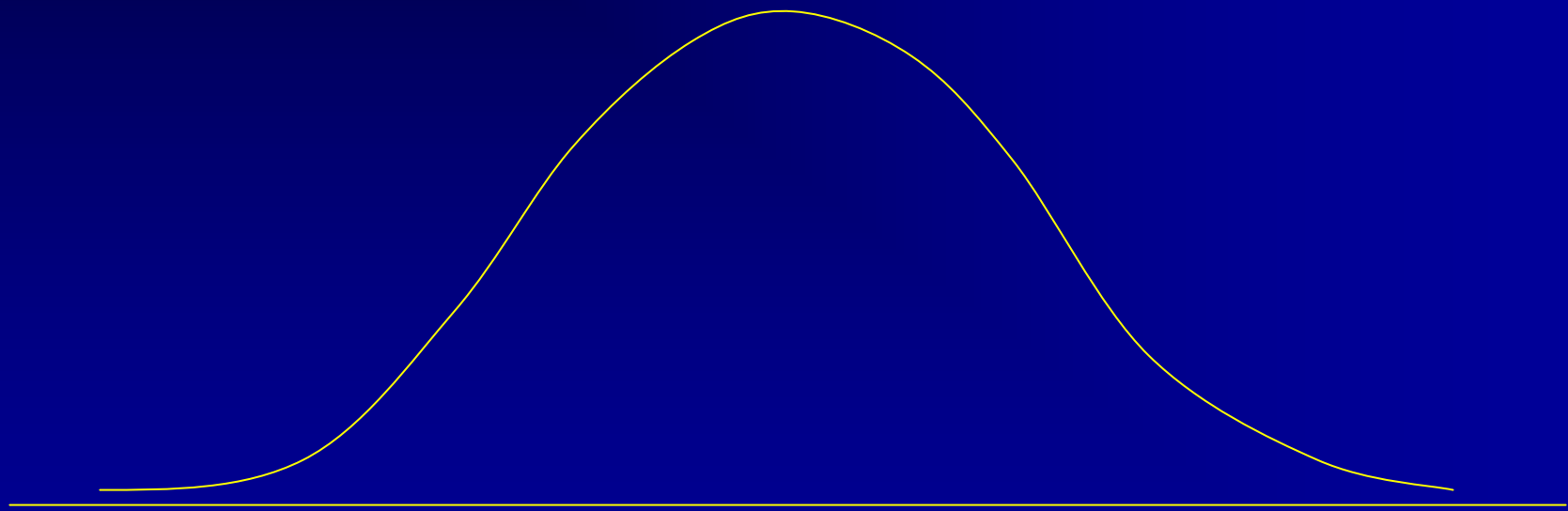
HCV Treatment Guideline Conundrum
Is Depression a Contraindication?

Van Thiel et al (1995)	Patients with psychiatric illness successfully treated with IFN
Pariante et al (1999)	Patients with preexisting lifetime or current psychiatric disorders no more likely than controls to stop IFN for psychiatric symptoms
Schaefer et al (2003)	Preexisting psychiatric disorders should not be considered a contraindication to IFN therapy

IFN, interferon.

Pariante et al. *Lancet.* 1999;354:131-132.
Schaefer et al. *Hepatology*. 2003;37:443-451.
Van Thiel et al. *Eur J Gastroenterol Hepatol*. 1995;7:165-168.

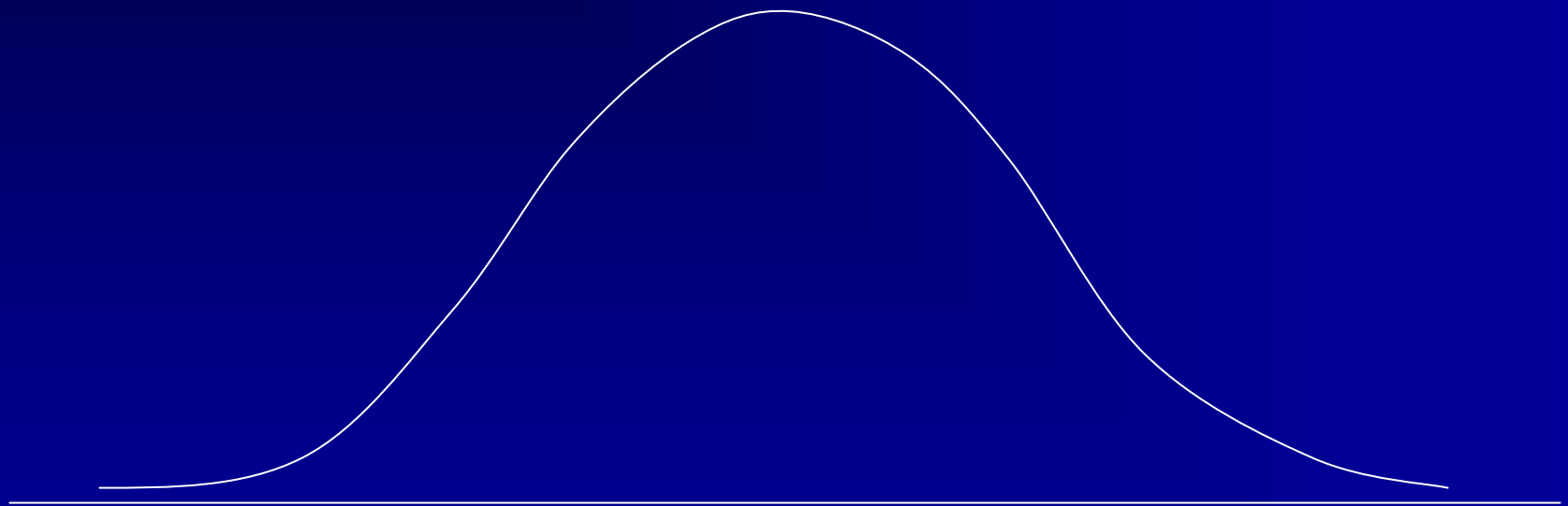
The Perspective of Dimension



The Perspective of Dimension

Future oriented
Function oriented
Consequence avoidant

Present oriented
Feeling oriented
Reward seeking



Introversion

Extraversion

Temperament and HCV

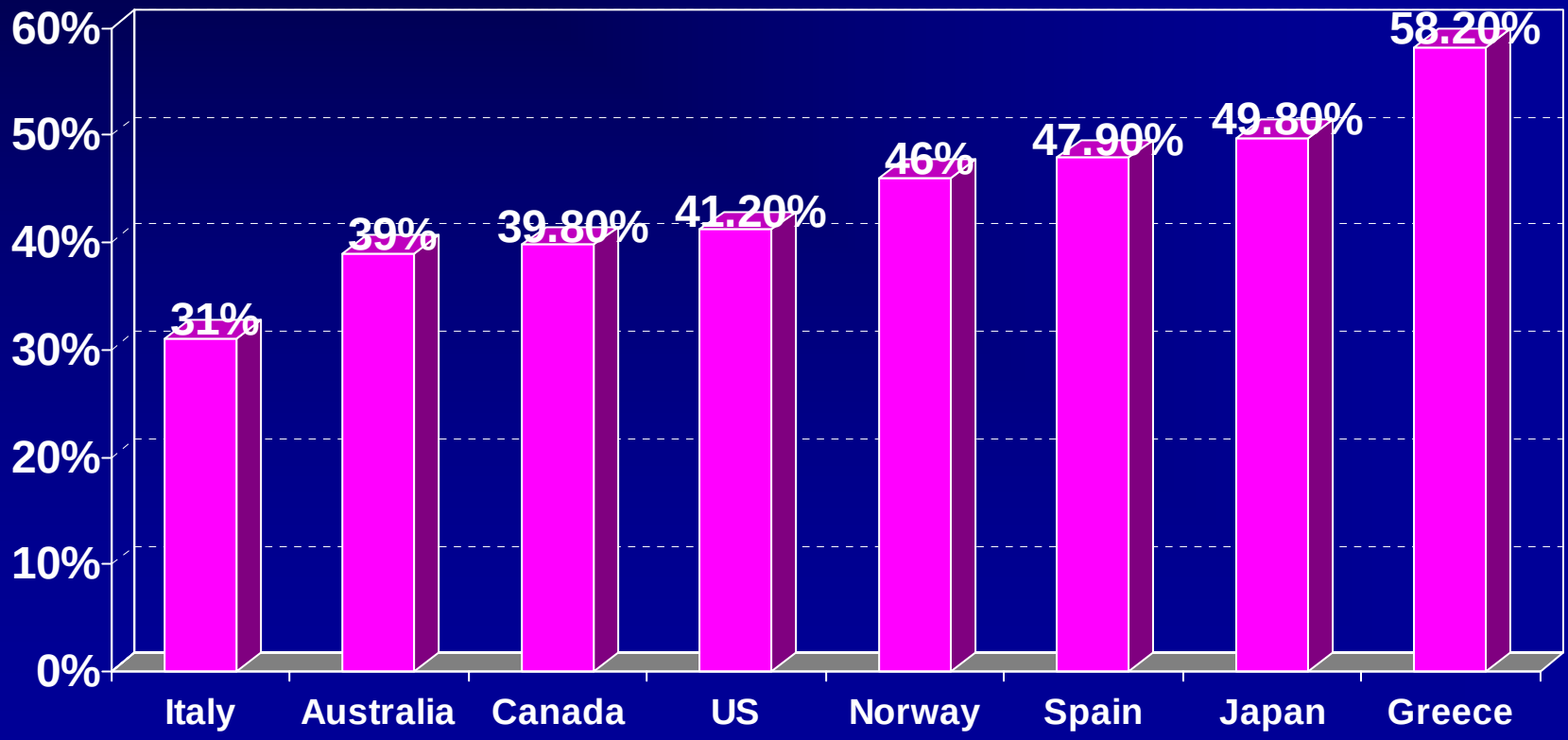
- No data on temperament measures or personality inventories have been published
- One might hypothesize that extraverts with low conscientiousness are at risk to engage in behaviors or be found in settings that might lead to transmission

Temperament and HCV

- Ko YC et al., 1992
  - tattoos associated with an OR of 5.9 (95%CI 1.6-22)
- Holsen DS et al., 1993
  - presence of tattoos associated with an OR of 5.44 (95%CI 1.68-9.21), independent of IVDU
- Delage G et al., 1999
  - tattooing associated with an OR of 5.7 (95%CI 2.5-13.0), independent of IVDU
- Haley RW et al., 2001
  - tattooing accounted for 41% of HCV+ patients presenting for orthopedic surgery

Temperament and HCV

Worldwide prevalence of HCV in correctional populations



Adapted from Reindollar RW, Am J Med, 1999.

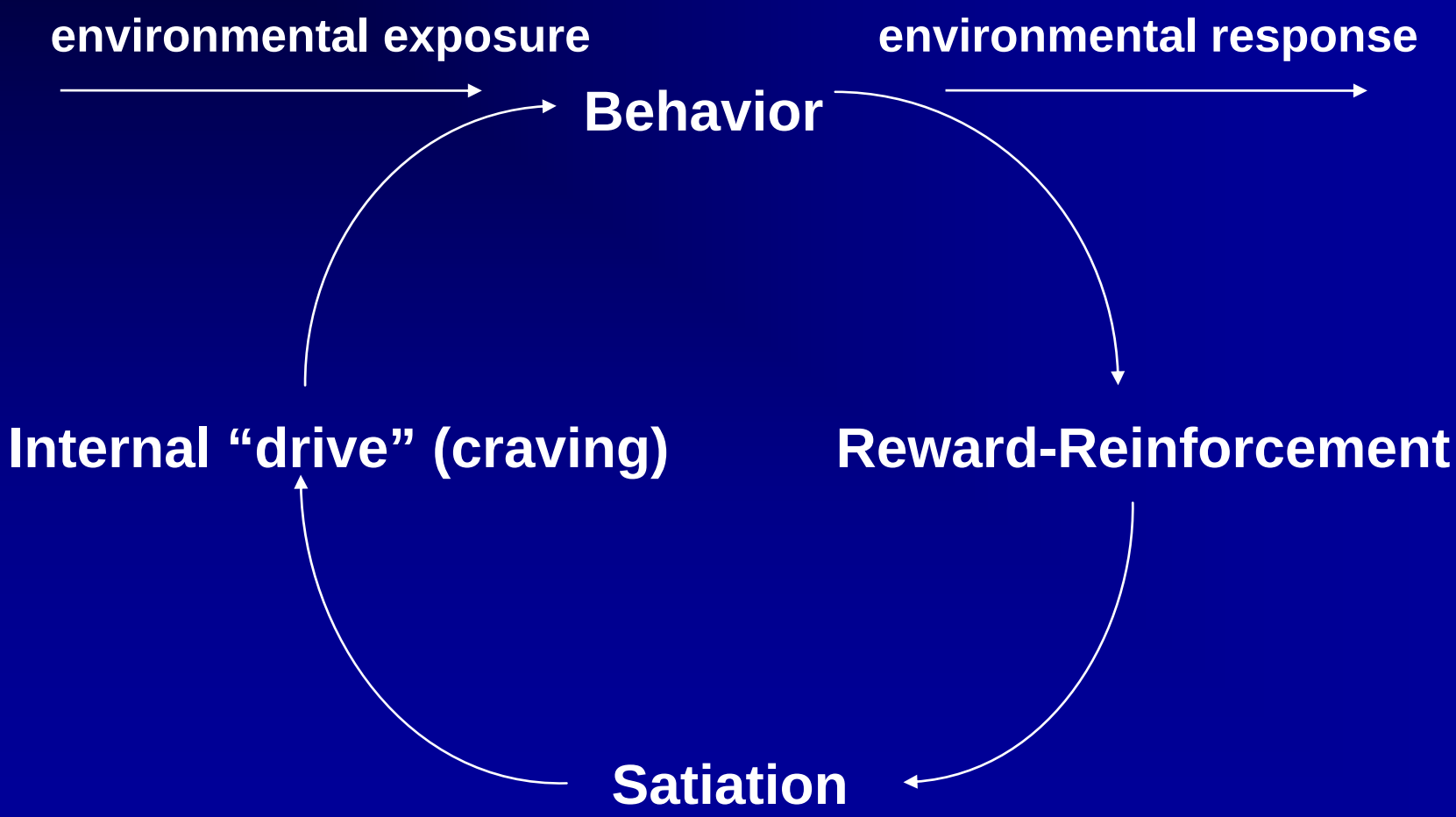
Substance Use Disorders and HCV

- Intravenous drug use is the main vector of HCV transmission
- Prevalence studies estimate that 60-90% of IVDU are anti-HCV^{+}
- HCV is more “efficient” than HIV
  - More IVDU become infected quicker

Alcohol and HCV Infection

- Alcohol use is associated with more liver disease in HCV patients
- Non-IVDU alcoholics have a higher prevalence of HCV than would be expected
  - Possible role of alcoholic liver damage in susceptibility to infection
  - Studies relied on self-report for routes of transmission

Motivated Behavior



Treatment of HCV in Patients With Substance Use Disorders

Backmund et al (2001)	SVR in 36% of injecting heroin users after detoxification SVR in 53% of methadone maintenance group patients
Schaefer et al (2003)	SVR in 43% of methadone group patients No patients in methadone group dropped out due to drug relapse
Sylvestre et al (2003)	SVR in 28% of methadone maintenance patients

SVR, sustained virologic response.

Backmund et al. *Hepatology*. 2001;34:188-193.
Schaefer et al. *Hepatology*. 2003;37:443-451.
Sylvestre et al. DDW. May 19-22, 2002; San Francisco, Calif.

Controversies in HCV Treatment

- Falck-Ytter et al, 2002
  - 293 patients with HCV
    - 83 (28%) treated – 11 (13% of treated) SVR
    - 98 (33%) not treated due to some psychiatric disorder
      - 71 (24%) not treated due to psychiatric contraindications
      - 27 (9%) not treated due to substance use disorder

Falck-Ytter et al., Ann Int Med, 2002; 136: 288-92.

“The struggle itself toward the heights
is enough to fill a man’s heart.
One must imagine Sisyphus happy.”

Albert Camus