

Neuropsychiatric Effects of Interferon-alpha:

Recognition and Management

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Criteria for DSM-IV Diagnosis of Major Depression

- Depressed mood and/or loss of interest that persists for ≥ 2 weeks
- 4 of the following associated symptoms (3, if both depressed mood and loss of interest are present)

Neurovegetative

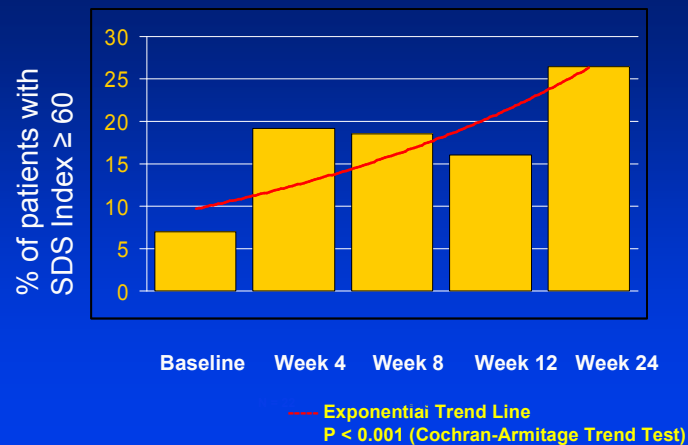
- Change in appetite or weight
- Insomnia/hypersomnia
- Fatigue/loss of energy
- Psychomotor agitation/retardation

Psychologic/cognitive

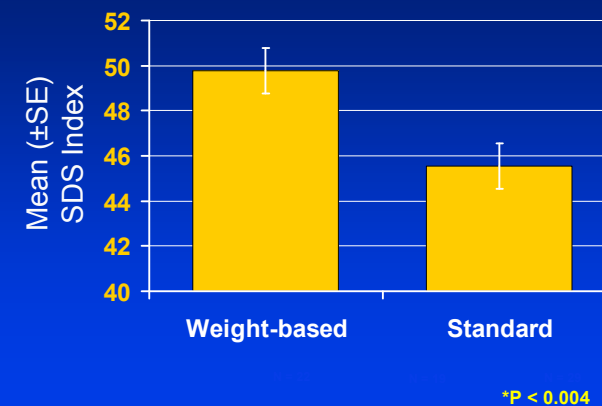
- Worthlessness or guilt
- Decreased concentration
- Suicidal ideation

APA. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. 1994.

Point Prevalence of Moderate/Severe Depressive Symptoms During PEG IFN/Ribavirin Therapy



Mean (\pm SE) SDS Index Scores During Treatment by Ribavirin Dose



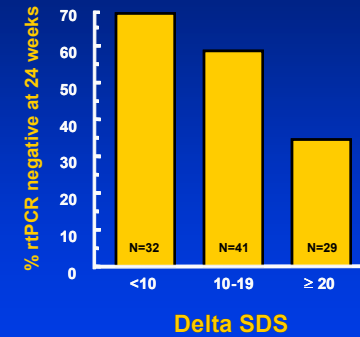
Risk Factors for the Development of Moderate/Severe Depression (SDS ≥ 60)

Risk Factor	Odds Ratio	95% Confidence Intervals
Controlling for baseline SDS Index Score		
Ribavirin Dosage*		
Weight based vs. standard dose	2.4	1.1 – 5.4
Not Controlling for baseline SDS Index Score		
Ribavirin Dosage**		
Weight based vs. standard dose	2.7	1.3 – 5.6

* p < 0.05
 ** p < 0.01

Raison et al. *J Clin Psychiatry*. In press

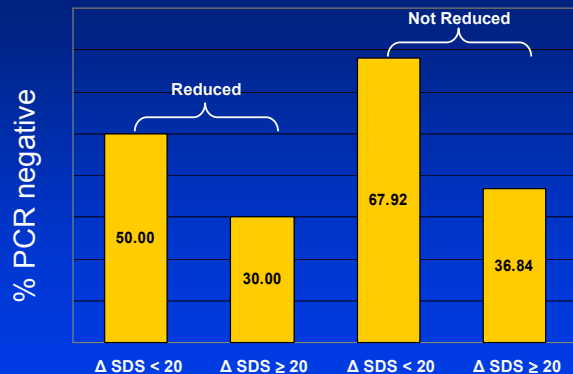
Depressive Symptoms and Viral Clearance at 24 weeks (n = 102)



Chi square=7.6, df=2, p<0.05

Raison et al. *Brain Behav Immun*. In press.

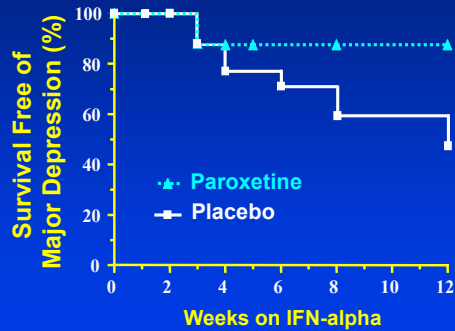
Depression and Success of Treatment at 24 weeks Controlling for Effect of Dose Reduction (n = 102)



Overview of Treatment Options for IFN-alpha-Induced Depression

- Pretreatment with antidepressant shown to significantly decrease development of depression with high-dose IFN alpha
- Recent studies suggest patients can be successfully treated once depression develops during IFN-alpha

Paroxetine Pretreatment Reduces the Incidence of Major Depression During the First 12 weeks of IFN-alpha



Musselman et al., *New England Journal of Medicine*, 344:961-966, 2001.

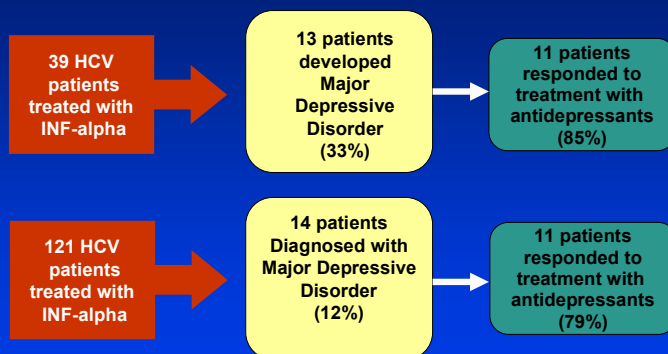
Antidepressant Prophylaxis in HCV Patients

Open, prospective trial of citalopram pre-treatment in patients on methadone maintenance who received pegylated IFN-alpha-2b:

- Citalopram pre-treatment associated with reduced IFN-alpha-induced "major depression" (14%) when compared to either methadone-maintained (64%) or non-psychiatric patients (55%) who did not receive antidepressant prophylaxis.

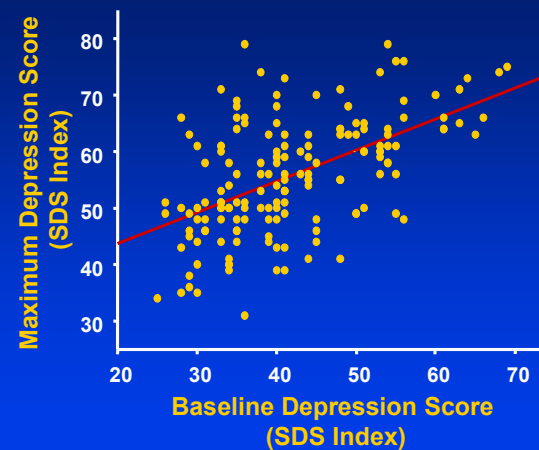
Schaefer et al., *Hepatology* 2003, abstract #333

Treatment of Major Depression in HCV patients Receiving IFN-alpha



Hauser et al. *Molecular Psychiatry*, 2002; 7(9):942-947.
Kraus et al. *Aliment Pharmacol Ther*, 2002; 16(6) 1091-9

Maximal Depression Scores During PEG IFN/ribavirin Therapy Are Highly Correlated with Depression Scores at Baseline



$Y=0.55X + 32.7$, $p<0.0001$ for slope, $r=0.54$; $p<0.0001$

Risk Factors for the Development of Moderate/Severe Depression (SDS \geq 60)

Risk Factor	Odds Ratio	95% Confidence Intervals
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Controlling for baseline SDS Index Score

History of Major Depression**	NS	
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Not Controlling for baseline SDS Index Score

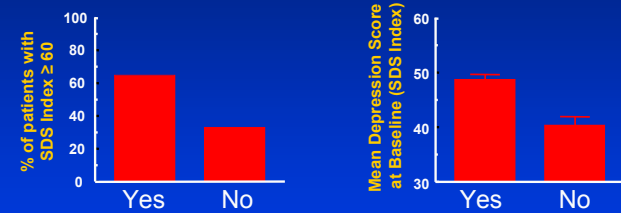
History of Major Depression**	3.3	1.3 – 8.1
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* $p < 0.05$

** $p < 0.01$

Raison et al. J Clin Psychiatry. In press

Patients with a past history of depression exhibited higher rates of becoming moderately to severely depressed during PEG IFN/ribavirin therapy and exhibited a higher depression scores at baseline



Past History of Depression

Chi Square=10.6, df=1, $p < 0.005$

Past History of Depression

$t=4.5$, $p < 0.0001$

Raison et al. J Clin Psychiatry. In press.

Algorithm for Prophylaxis vs. Symptomatic Treatment

Prophylaxis:

- Mild or greater depressive/anxiety symptoms just prior to IFN initiation
- Receiving ongoing treatment for a psychiatric condition
- Developed psychiatric symptoms during prior IFN treatment
- Patient requests prophylaxis

Symptomatic Rx:

- No depressive/anxiety symptoms prior to IFN treatment
- No past psychiatric history
- Tolerated prior IFN treatment without psychiatric side effects

Raison et al., CNS Drugs, in press

Management of Psychiatric Side Effects: General Considerations

- During therapy, evaluate patients for depression at each follow-up visit
 - Consider use of standardized rating scales (Inventory of Depressive Symptomatology (*our favorite*), Beck Depression Inventory, Inventory of Zung Self Rating Depression Scale, CES-D)
 - “Have you felt depressed recently?”
- Ongoing counseling and support are essential
- Work closely with patient’s psychiatrist/counselor
- Renew next month’s supply of IFN only when he/she shows up for appointment and is stable

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Psychologic/cognitive

- Worthlessness or guilt
- Decreased concentration
- Suicidal ideation

APA. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. 1994.

“Take Home” Message

- For almost all patients with IFN-alpha-induced neuropsychiatric side effects, it is likely that any antidepressant you choose will be better than no antidepressant at all,
- Start antidepressant at low dose, especially in patients with anxiety, panic and/or somatic side effects
- Achieve therapeutic dose for adequate treatment period

General Side Effects of Newer Antidepressants

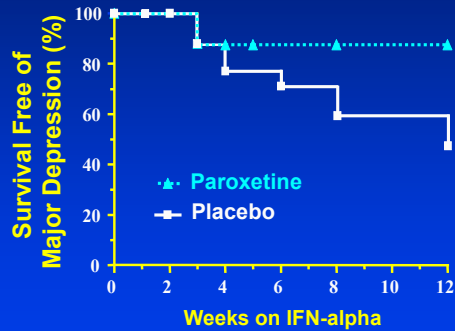
- “Selective” Serotonin Reuptake Inhibitors (SSRIs)
 - Anxiety, GI complaints, insomnia, sexual problems, sweating, headaches, weight gain (long-term use), significant drug-drug interactions (except citalopram)
- Venlafaxine (EffexorXR)
 - GI complaints, anxiety, sexual problems, sweating, headaches, low rate of increased BP (above 300 mg/d)
- Duloxetine (Cymbalta)
 - Side effects similar to SSRIs except increased nausea early in treatment and potentially decreased sexual dysfunction compared to SSRIs. Not recommended in decompensated liver disease.
- Mirtazapine (Remeron)
 - Significant weight gain, somnolence, rare agranulocytosis, no sexual side effects, sleep promoting

Specific Concerns in Patients Receiving IFN-alpha/ribavirin

- Serzone has very low incidence (1 in 300,000) of fulminate liver failure, but no evidence HCV patients at increased risk
- Bupropion may be associated with slightly increased risk of seizures in patients receiving IFN-alpha.
- Newer antidepressants safe in patients with liver disease. If hepatic function is compromised, blood levels of antidepressants (and all hepatically metabolized drugs) will be increased. Benzodiazepines may worsen hepatic encephalopathy.

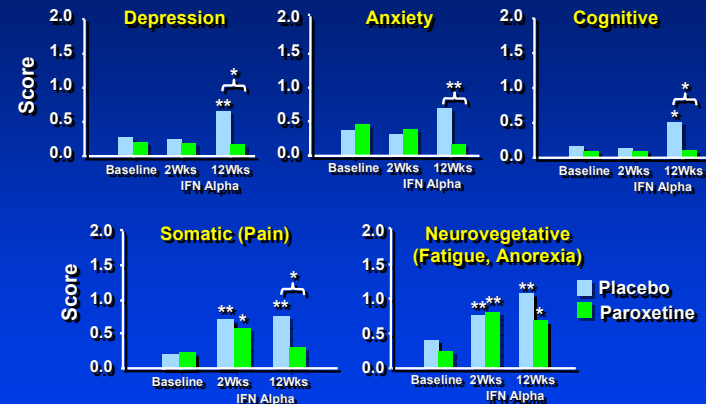
JAMA 2002; 287(9), 1103; Ahmed et al., Hepatology 2003; Demolis et al., Brit J Clin Pharmacol 1996; Joffe et al., Eur J Clin Pharmacol 1998; Raison et al., CNS Drugs, in press.

Paroxetine Pretreatment Reduces the Incidence of Major Depression During the First 12 weeks of IFN-alpha



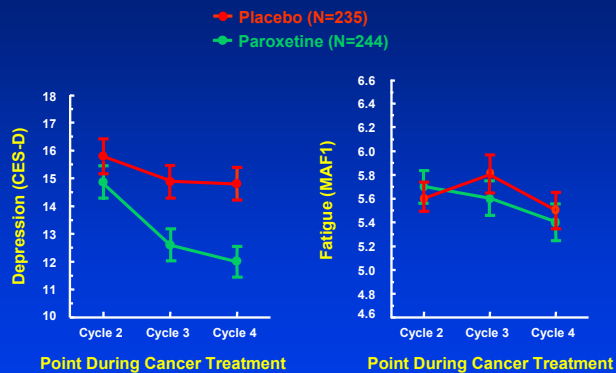
Musselman et al., *New England Journal of Medicine*, 344:961-966, 2001.

Symptom Dimensions and AD Response



Data given as mean +/- SEM: *P = .05, **P = .01
 Capuron L, et al. *Neuropsychopharmacology*, 2002, in Press.

Reduced Antidepressant Responsiveness of Fatigue In Patients with Cancer



Morrow et al. *Journal of Clinical Oncology*, 21:4635-4641, 2003.

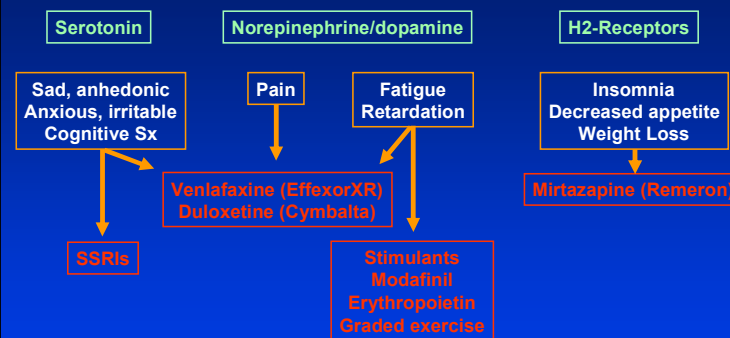
- Most commonly reported symptom, bordering on 100% with chronic treatment
- Worsens as treatment progresses
- Frequently unresponsive to rest
- Difficult to treat
- Symptom most often cited in treatment discontinuation in some studies

Neurovegetative Symptoms and Catecholamines

- **Fatigue**
 - TCAs more effective than SSRIs in CFS
 - Modafinil and psychostimulants decrease fatigue in normals and improve fatigue in HIV, MS and MDD
- **Pain**
 - TCAs out perform fluoxetine for neuropathic pain in non-depressed patients. FLUOX = placebo
 - Venlafaxine, bupropion and duloxetine demonstrate analgesic effects
- **Conclusion:**
 - Although no studies have been done in IFN-alpha treated patients, medical literature suggests that catecholamine agents (psychostimulants, modafinil, bupropion, venlafaxine) might be more effective than SRIs for fatigue and pain

Vercoulen et al, Lancet 1996; Pigeau et al, J Sleep Res 1995; Breitbart et al, Arch Int Med 2001; Rammohan et al, J Neurol Neurosurg Psychiatry 2002; Prakash et al, Depression & Anx 1998; Max et al, NEJM 1992; Semenchuk et al Neurology 2001; Sindrup et al, Neurology 2003; Detke et al, J Psychiatric Res 2002

Targeting Treatment to Specific Depressive-Spectrum Symptoms



Capuron et al. Neuropsychopharm 2002; 26(5): 643-52; Morrow et al. J Clin Oncol 2003; 21(24): 4635-41; Grothe et al. Pharmacother 2004; 24(5): 621-9; Fava et al. J Clin Psychiatry 2004; 65(4): 521-30; Entsuah R, Yisheng L. APA Annual Meeting 2003; Breitbart et al. Arch Int Med 2001; 161(3): 411-20; Schwartz et al. Onc Nursing Forum 2002; 29(7): E85-90; DeBattista et al. J Clin Psychopharm 2004; 24(1): 87-90; Kast. Sup Care Cancer 2001; 9(6): 469-70; Max et al. NEJM 1992; 326(19): 1250-6

Irritability

Many patients receiving IFN-alpha report increased irritability which often interferes with work and social relationships

- Irritability/anger symptoms increased from 11.3% to 24.5% during treatment with IFN-alpha-2b and IFN-alpha-2 plus ribavirin. No increase in HCV+ comparison group
- Pegylated IFN-alpha-2b: 35% irritability
- Pegylated IFN-alpha-2a: 24% irritability

Kraus et al., J Clin Psychiatry 2003; Manns et al., Lancet 2001; Fried et al., N Eng J Med 2002

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Where is irritability?

APA. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. 1994.

Criteria for a DSM-IV Diagnosis of Manic Episode

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting ≥ 1 week (or any length of time if hospitalized)
- ≥ 3 of the following symptoms (4 if only irritable)
 - Inflated self-esteem/grandiosity
 - Decreased need for sleep
 - More talkative/pressure to talk
 - Flight of ideas/racing thoughts
 - Increased goal-directed activity
 - Excessive involvement in pleasurable activities with high potential for painful consequences

Irritability is technically a symptom of mania!

APA. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. 1994.

Mania and IFN-alpha

- IFN alfa has been repeatedly observed to cause mania in case reports and series
- In 95 treatment-naïve patients receiving pegylated IFN-alpha-2b plus ribavirin for 24-48 weeks, 20% developed manic/hypomanic episodes, an additional 23% developed "major depression with manic features".
- Clinical experience suggests most manic presentations are dysphoric/irritable rather than euphoria, consistent with other immune-related manic conditions, i.e. HIV
- IFN-alpha withdrawal manias also reported

Why Does it Matter?

- All antidepressants appear capable of inducing manic episodes; rate is up to 30% in bipolar patients. Bipolar disorder may be an unrecognized comorbidity in patients with HCV
- TCAs have highest rates of mania induction

Onyike et al., *Am J Psychiatry* 2004; Hosoda et al. *Psychiatry Clin Neurosci*. 2000; Altshuler et al., *Am J Psychiatry* 1999.

Major Depressive Episode

Unhappy
Decreased appetite/weight
Decreased sleep
Poor concentration
Suicidal ideation
Fatigue

Dysphoric Mania

Unhappy
Decreased appetite/weight
Decreased sleep
Poor concentration
Suicidal ideation
Fatigue

IRRITABILITY

Differentiating Dysphoric Mania from Depression During IFN-alpha Rx

- | | |
|-------------------------------|---------------------------------------|
| • Rage | • Mild irritability |
| • Poor Insight into condition | • Good insight into condition |
| • Increased energy | • Fatigued |
| • Hypersexuality | • Loss of sexual interest |
| • Grandiose plans | • Diminished expectations |
| • Increased speech production | • Diminished speech production |
| • Increased rate of speech | • Decreased rate of speech |
| • Increased use of telephone | • Decreased desire for social contact |
| • Flamboyant style of dress | • Drab clothing |
| • Psychosis relatively common | • Psychosis relatively uncommon |

Treatment of IFN-alpha-Induced Irritability

Clinical experience suggests that most cases of IFN-alpha-induced irritability respond to antidepressant treatment

Paroxetine significantly decreased irritability/anger in 14 patients who developed depression during IFN-alpha treatment. Why?

- Anger/irritability correlates with development of depressive symptoms during IFN-alpha treatment
- Major depression is often associated with irritability
- Anger/irritability correlates with low 5HT functioning: IFN-alpha reduces TRP availability
- SRIs have been shown to reduce anger/irritability/poor impulse control/aggression in normal controls, personality disorders, PTSD, major depression, smoking cessation, traumatic brain injury

Kraus et al., Aliment Pharmacol Ther 2002; Akiskal et al., Arch Gen Psychiatry 1993

Treatment of Mania

- Full mania is a clinical emergency, usually requiring hospitalization
- IFN alfa should be stopped immediately
- Antidepressants can cause and/or worsen mania
 - They should be stopped immediately

Treatment of Mania (cont'd)

- Acute treatments
 - Neuroleptics
 - Olanzapine (Zyprexa®) 15–30 mg QD
 - Risperidone (Risperdal®) 2–6 mg QD
 - Mood Stabilizers
 - Valproic acid (Depakote®) can be loaded at 1.5–2 g QD; blood level should be >45 ng/dL
 - Lithium average dose 900–1800 mg QD; blood level between 0.8–1.2 mEq/L. Very toxic in overdose
 - Carbamazepine (Tegretol®) can significantly lower blood levels of ART meds
 - Benzodiazepines
 - Preferred agents clonazepam (Klonopin®) or lorazepam (Ativan®); dose to symptomatic control