Pharmacological aspects
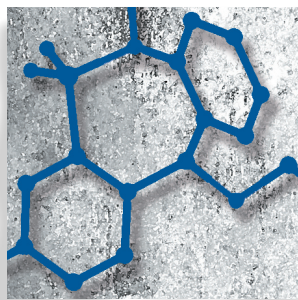
Major depression during interferon-α treatment: vulnerability and prevention

Francis E. Lotrich, MD, PhD

Major Depressive Disorder (MDD) during interferon-α (IFN–α) treatment can occur within a few months of therapy, and shares many homologies with other forms of MDD. Most patients are resilient to the side effect of interferon-induced depression (IFN-MDD), but 15% to 40% are vulnerable. Several studies have employed antidepressants to prevent the incidence of an IFN-MDD episode, and the results suggest that prophylactic antidepressants may be specifically useful in those with pre-existing subthreshold depressive symptoms and/or a history of prior MDD episodes. Several other potential markers of vulnerability for IFN-MDD have been implicated in assessments of nondepressed patients before they start IFN–α. These include poor sleep quality, premorbid elevations in inflammatory cytokines, genetic polymorphisms in the serotonin system, personality, and social support. The interplay of these factors strongly predicts who is at risk for IFN-MDD, and indicates several potentially modifiable targets for the personalized prevention of IFN-MDD.

Keywords: *depression; cytokine; interferon; prevention; resilience; genetics*

Author affiliations: Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, USA

Address for correspondence: Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA
(e-mail: lotrichfe@upmc.edu)

Major Depressive Disorder (MDD) is common, costly,[1-3] and notably heterogeneous. Unfortunately, the accurate prediction and subsequent prevention of MDD episodes (MDEs) has been challenging. There is evidence that MDEs are variously associated with elevated psychosocial stress, the postpartum period, hypothyroidism, circadian changes, cerebrovascular disease, administration of inflammatory cytokines such as interferon-α (IFN−α), etc. Therefore, one approach for preventing a MDE could be to avoid stressful circumstances, pregnancy, cerebrovascular disease, and/or IFN−α therapy. However, this is often impractical. Thankfully, most people who are exposed to these various "triggers" do not develop MDD.

Identifying modifiable markers of risk in specifically vulnerable people, and then mitigating these before MDD occurs, could be a better approach for preventing MDD. However, identifying causal risk factors that pre-exist in nondepressed people requires prospective studies, and the incidence of an MDE over 1 year is less than 2%.[4-6] The necessarily large epidemiologic studies have successfully identified predictive risk markers such as gender, age, cohort, family history, marital status, socioeconomic status, and stressful life events[6,7]— but each of these is difficult or impossible to mitigate. Another strategy is needed for prospectively assessing nondepressed people for modifiable risk factors, and a related strategy is needed for examining whether specifically alleviating these vulnerabilities prevents MDE.

Pharmacological aspects

Selected abbreviations and acronyms

IFN-α   *interferon-alpha*
IL   *interleukin*
MDD   *major depressive disorder*
SSRI   *selective serotinin reuptake inhibitor*

MDD during IFN-α therapy

One approach for delineating modifiable risk factors is to examine homogeneous groups of people who are definitively known to soon be exposed to a specific MDD-evoking situation. Towards this end, patients receiving IFN−α may be ideal candidates for examining MDD vulnerability.[8-12] MDD during IFN−α treatment (IFN-MDD) typically develops within the first 2 or 3 months of administration,[13-17] and occurs in about 15% to 40% of patients.[18] Thus, prospectively assessing IFN-MDD onset is feasible—and consequently it may be possible to determine predictive modifiable vulnerabilities in the 15% to 40% who subsequently develop IFN-MDD.

Of course, it is conceivable that IFN-MDD is unique, and that other forms of MDD are completely distinct from it. However, several lines of evidence indicate that IFN-MDD may successfully inform us about MDD in general. First, a variety of studies have found a robust relationship between IFN−α and MDE, including those demonstrating a dose-response relationship,[19,20] studies with control groups,[16,19-21] and prospective documentations of worsening depression during IFN−α treatment with a return to baseline mood after discontinuation.[23-25] Thus, IFN-MDD is a replicable finding in prospective studies. Second, IFN-MDD has phenomenological resemblance to MDD diagnosed in other situations.[21-24] That is, IFN-MDD is not simply fatigue and malaise but—similarly to MDD—involves anhedonia, depressed mood, irritability, anxiety, social withdrawal, poor concentration, altered sleep, personality changes, and suicidal ideation *(Table I)*. Third, MDD and IFN-MDD may share similar pathophysiologic mechanisms, as indicated by various independent lines of investigation:

- Many inflammatory cytokines are elevated during MDD.[51-53]
- Psychosocial stress can increase the levels of inflammatory cytokines.[54,55]
- IFN−α and other cytokines can affect central monoaminergic systems plausibly involved in MDD.[56-63]
- Peripheral cytokines and IFN−α have access to the CNS through a variety of routes in addition to being synthesized in the brain.[64-66]
- Endogenous IFN−α mRNA can be induced in the cortex, hippocampus, and hypothalamus, with correlated changes in behavior in animal models of depression.[64,67]
- Systemic administration of IFN−α and other cytokines can affect amotivation and anhedonia behaviors in rodent models of depression.[68-75]
- Once IFN-MDD is diagnosed, it responds to treatments that are effective for idiopathic MDD, ranging from selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants to electroconvulsive therapy,[15,76-85] with about 79% to 85% of patients responding to antidepressants.[86,87]
- IFN−α administration can influence frontal lobe and anterior cingulate function,[88,89] dopaminergic activity,[60] and serotonergic function,[90-93]—all of which may contribute to the development of depression in a manner homologous to other types of MDD.

Of further public health significance, the use of IFN−α is not rare. Almost 2% of the U.S. currently has chronic hepatitis C (HCV).[94] IFN−α is the only FDA-approved treatment for HCV,[95,96] whereas about 170 million people worldwide have been infected with HCV.[97] Supporting IFN−α's widespread use, untreated chronic HCV can lead to cirrhosis, hepatocellular cancer, and liver failure,

Signs and symptoms	MDD	IFN-MDD
Anhedonia	Yes	Yes[24-29]
Depressed mood	Yes	Yes[26-30]
Sleep problems	Yes	Yes[26,27,29-32]
Amotivation	Yes	Yes[27]
Decreased appetite	Yes	Yes[27,28,30]
Concentration changes	Yes	Yes[27-29,33-36]
Tearfulness	Yes	Yes[27]
Social withdrawal	Yes	Yes[27]
Guilt	Yes	Yes[26]
Interpersonal sensitivity	Yes	Yes[37]
Suicidal ideation	Yes	Yes[27,29,38]
Associated symptoms		
Irritability	Yes	Yes[26,27,29,30,39]
Increased neuroticism	Yes[40,41]	Not known
Care-seeking behaviors	Yes[42]	Seen in illness behavior[43]
Dependency/acting out regression/somatization	Yes[44,45]	Seen in illness behavior[46-50]

Table I. Comparison of Major Depressive Disorder (MDD) and interferon-α depressive disorder (IFN-MDD) during interferon-α treatment.

resulting in about 10 000 deaths per year in the US,[98] a rate which exceeds that from acquired immunodeficiency syndrome.[99] Unfortunately, IFN-MDD can potentially result in suicide,[38] dose reduction with risk for viral relapse,[16] discontinuation of treatment,[100,101] and lower quality of life.[102,103] Therefore, the two rationales for preventing IFN-MDD are that (i) this is a common and disabling syndrome; and (ii) it may be and ideal strategy for informing us about ways to prevent MDD in general.

Prevention studies of IFN-MDD

A few prophylactic trials using selective serotonin reuptake inhibitors (SSRIs) have transpired. These prevention studies initiated SSRIs in patients who were not currently experiencing any MDE prior to beginning the IFN–α therapy *(Table II)*.[80,83,85,104-107] The first randomized placebo-controlled trial (RCT) was done in patients with metastatic melanoma, using very high doses of intravenous IFN–α. This initial study found strong evidence for prevention of IFN-MDD, with only 2/18 paroxetine-treated patients (11%) developing IFN-MDD, as compared with 45% of the placebo-treated group.[80] Similarly, in three open-label trials of prophylactic SSRIs given to nondepressed HCV patients, only 3/32 patients (9%) developed IFN-MDD, despite all 32 patients having a prior history of affective disorder. These open-label studies are thus consistent with this RCT study, supporting the conclusion that preventative treatment with SSRIs may be useful.

However, two small RCT studies have now been completed in patients with HCV *(Table II)*. Neither study found IFN-MDD prevention.[85,106] Prophylactic SSRIs may therefore not be universally effective. Despite these two negative findings, one of these studies did report that 24/29 patients in the placebo group developed elevated depression symptoms compared with 10/23 in the paroxetine group.[106] Additionally, further exploratory analyses indicated that prevention may have been most successful for those subjects who already had high pretreatment baseline levels of depressive symptoms.[106] This would be an example of "indicated prevention" whereby treating "subthreshold" depression symptoms may prevent subsequent worsening to full categorical MDD.[108-111] It has been well-replicated that higher levels of pretreatment depression symptoms are associated with the development of IFN-MDD,[18,112-115] and these subthreshold symptoms may be an appropriate target for using preventive SSRIs. Another open possibility is that prophylactic SSRIs specifically prevented IFN-MDD in those with past histories of MDD in remission. This type of prevention would be consistent with the use of antidepressants to prevent recurrence of remitted MDD.[116-119]

To explore this latter possibility, we prospectively followed 31 patients who were not depressed at the onset of IFN–α therapy (as determined using a Structured Clinical Interview of DSM-IV Axis I diagnoses). All of these patients had no MDEs within 6 months prior to starting IFN–α, but they did have a history of past MDD. Ten of these patients were stably taking SSRIs. Only 20% (2/10) of the patients on SSRIs developed IFN-MDD, while 47.6% (10/21) not on antidepressants did. These results are numerically similar to the RCTs reviewed above. This very limited analysis suggests a

SSRI	Trial type	(N)	Baseline characteristics	Diagnosis	Comments
Paroxetine[80]	RCT	18 vs 20	Melanoma patients; average HAM-D>5	DSM-IV	Prevented IFN-MDD. 2/18 vs 9/20
Paroxetine[85]	RCT	14 vs 19	Average HAM-D<3	DSM-IV	Did not prevent IFN-MDD. 5/14 vs 6/19
Paroxetine[106]	RCT	23 vs 29	Median MADRS = 3	DSM-IV or MADRS>15	Did not prevent IFN-MDD overall 3/23 vs 6/29 Benefit for patients with baseline MADRS >3
Citalopram[104]	Open label	10 vs 0	MDD history in remission	HAM-D =17	1/10 had recurrence of IFN-MDD
Paroxetine or Citalopram[120]	Open label	8 vs 0	History of previous IFN-MDD (Comparison with prior IFN–α trial)	HADS>8	0/8 had recurrence of IFN-MDD Small average increase in HADS scores
Citalopram[107]	Open label	14 vs 11	Average MADRS >10; History of affective disorder	DSM-IV	2/14 developed IFN-MDD vs 7/11 in the comparison group
Various	Open label	10 vs 21	History of any DSM-IV affective disorder	DSM-IV	2/10 developed IFN-MDD vs 10/21 in the comparison group

Table II. Studies examining prevention of IFN-MDD using antidepressants. Three randomized placebo-controlled trials (RCT), and four open-label studies examining the prevention of major depressive disorder (MDD), diagnosed using criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV (DMS-IV), the Hamilton Depression rating scale (HAM-D), or the Montgomery-Asberg Depression Rating Scale (MADRS).

more targeted use of SSRIs to prevent recurrence, limiting prophylactic SSRI to those patients who are known to have past MDD histories.

However, all of these studies have been very limited in size, and therefore power. Assessing all of the six published prevention studies and our open-label data combined—in a very exploratory type of meta-analysis—15/97 (15%) patients receiving SSRIs prior to starting IFN–α developed IFN-MDD, compared with 36/99 (36%). This is a significant difference, χ^2=8.2; P<0.001. However, limiting the meta-analysis to the three RCTs, 10/55 (18%) subjects randomized to pretreatment paroxetine developed IFN-MDD while 21/68 (31%) randomized to placebo did. The trend is numerically similar to the larger meta-analysis, but does not have the power to be significant in a chi-square test (χ^2=1.98).

At this point, only tentative conclusions are possible: (i) Prophylactic SSRIs may plausibly cut in half the incidence of IFN-MDD. To conclusively determine this, however, will require a larger-size trial than those performed to date; (ii) SSRIs may specifically benefit subjects with either pre-existing depressive symptoms (ie, subthreshold depression) and/or a history of prior MDD. This is consistent either with studies of "indicated prevention" in which patients with subthreshold depression are prevented from worsening to full categorical MDD by about 30%,[108-110] or with studies preventing recurrence of MDD.[116-119] A more targeted prevention RCT would be valuable to examine these two possibilities; (iii) Even if SSRIs are found to be effective prophylactics for some people, about 15% to 20% of patients still developed IFN-MDD even when prescribed SSRIs, therefore antidepressants may not be universally effective. Other targets and approaches for prevention are needed; (iv) Most importantly, about half of the patients with a history of MDD remain resilient even during IFN–α treatment. Identifying the source of this resilience for potential replication in other patients would be beneficial.

Modifiable risk factors for IFN-MDD

The goal for this work is preventative treatments that can be targeted towards specifically mitigating those mechanisms underlying vulnerability. Poor sleep quality prior to IFN–α treatment may be one such risk factor.[121,122] Patients with scores greater than 10 on the Pittsburgh Sleep Quality Index, a validated self-report assessment of sleep quality,[123] were ten times more like

to subsequently develop IFN-MDD than patients sleeping better than this.[122] This large effect size was evident even when controlling for other depression symptoms. It is also consistent with large epidemiological studies wherein insomnia predicted the subsequent development of MDD over follow-up intervals of 1 to 35 years.[124-127] As many treatments for sleep exist, this may be a potentially modifiable risk factor for preventing IFN-MDD. This has previously been suggested for MDD,[128] but may now be readily testable in patients about to be treated with IFN–α.

There is also evidence that increased age may be another risk factor for IFN-MDD,[129] although this is certainly not a consistent finding.[130,131] Despite the fact that age itself is not modifiable, this could indicate the presence of age-related modifiable risk factors. Related to this, elevated levels of inflammatory cytokines, such as interleukin-6 (IL-6), prior to IFN–α therapy have been associated with subsequent IFN-MDD.[132,133] Additionally, a polymorphism in IL-6 that has been associated with increased IL-6 levels is predictive of IFN-MDD.[134] In the subset of people with increased IL-6 during IFN–α administration, the IL-6 levels temporally predicted next month's depression symptoms.[133] This is consistent with cross-sectional studies in which elevated IL-6 levels are associated with MDD.[54,132,135-140] Thus, increased IL-6 may be another plausibly modifiable target for preventive intervention in depressed individuals. Interestingly, IL-6 increases with age but can be modified by diet[141] and/or exercise.[142,143] Potential premorbid risk factors for IFN-MDD that may be modifiable through psychosocial interventions could include social isolation[144] and neuroticism.[115,145] However, when controlling for other premorbid risk factors, the effect size for these is fairly small.[146] Another risk factor may be a hyperactive stress response in the hypothalamic-pituitary-adrenal (HPA) axis.[147] Given the common association between abnormalities in the HPA axis and MDD,[148-150] this may also be a potentially useful predictive marker. Interestingly, HPA axis responsiveness can be therapeutically modifiable by antidepressants.[151-154] It is therefore plausible that patients with overactive HPA responses may be the subjects who benefit most from antidepressant prophylaxis. Consistent with this, stress-reactivity did correlate with depressive symptoms prior to IFN–α therapy[147]—and thus elevated stress-reactivity may be a potential predictor of the need for "indicated" SSRI prevention.

Genetic polymorphisms within the serotonergic system have also been associated with vulnerability to IFN-

MDD.[134,146,155] Two studies have replicated the finding that a short allele in the serotonin transporter robustly increases risk for IFN-MDD.[134,146] Vulnerability to tryptophan depletion has also been associated with polymorphisms in the 5-HT reuptake transporter.[59] Because IFN-MDD has been associated with lowered tryptophan levels during treatment,[57,91,93,156] this suggests that differences in serotonergic tone may leave some people vulnerable to IFN-MDD. It is also plausible that these are the same subjects who may benefit from SSRI prophylaxis, a possibility that requires testing.

Interestingly, gender has not been a consistent predictor of IFN-MDD,[37,157,158] which suggests that IFN-MDD may be partially distinct from some forms of MDD that are unique to females. Also, as long as patients remain abstinent, a past history of drug and alcohol abuse is not predictive of increased risk.[15,37,131] This suggests that risks for drug and alcohol abuse are distinct from risk for IFN-MDD. One critical implication is that a past history of drug use, in remission, is not a contraindication to prescribing IFN−α. Nonetheless, several leads are now suggested by these various predictive risk factors, several of which may be amenable to modification. The IFN-MDD paradigm has now been used in several studies to examine whether SSRIs can prevent depression. It may now be useful to determine whether other preventive treatments are effective.

Other populations at selective risk for MDD

In summary, encouraging results indicate that: (i) specific patients may be at elevated risk for IFN-MDD; (ii) this vulnerability may be identifiable prior to IFN−α treatment; (iii) some sources of this vulnerability (such as poor sleep) may be modifiable; and (iv) therefore personalized prevention is testable and could become a reality. Because of the high incidence of IFN-MDD in the first few months of treatment, and the ability to recruit nondepressed patients prior to IFN−α treatment, examining these possibilities appears to be practical and feasible in this population. Several studies with prophylactic SSRIs have already occurred. Furthermore, because of the homologies between IFN-MDD and MDD in general, any lessons learned from IFN-MDD may be translatable to other types of MDD. As examples, MDD occurs at higher rates in populations with multiple chronic illnesses,[159] during bereavement,[160] in caregivers of demented patients,[161] in stroke survivors,[162-164] in postpartum mothers,[110,165,166] and there is preliminary evidence that MDD incidence could potentially be reduced in these settings.[161,167] Similar to IFN-MDD, most people in these settings are resilient to developing MDD, with only a subset who are vulnerable.[168]

Conclusion

It remains an intriguing possibility that modifiable risk factors identified for IFN-MDD may also be modifiable risk factors in these other settings. Thus, targeting the appropriate prevention to the appropriate patient may be possible, and this may soon lead to the personalized prevention of MDD. ❏

REFERENCES

1. Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. *Arch Gen Psychiatry*. 1999;56:39-44.
2. Coyne JC, Fechner-Bates S, Schwenk TL. Prevalence, nature, and comorbidity of depressive disorders in primary care. *Gen Hosp Psychiatry*. 1994;16:267-276.
3. Stoudemire A, Frank R, Hedemark N, Kamlet M, Blazer DG. The economic burden of depression. *Gen Hosp Psychiatry*. 1986;8:387-394.
4. Patten SB. Long-term medical conditions and major depression in a Canadian population study at waves 1 and 2. *J Affect Dis*. 2001;63:35-41.
5. Blazer DG. Mood disorders: Epidemiology. In: Sadock BJ, Sadock VA, eds. *Comprehensive Textbook of Psychiatry*. 7th ed. Philadelphia, PA: Lippincott Williams & Williams; 2000:1298-1307.
6. Eaton WW, Kramer M, Anthony JC, Dryman A, Shapiro S, Locke BZ. The incidence of specific DIS/DSM-III mental disorders: data from the NIMH Epidemiologic Catchment Area Program. *Acta Psych Scand*. 1989;79:163.
7. Hagnell O, Lanke J, Rorsman B, Ojesjo L. Are we entering an age of melancholy? Depressive illnesses in a prospective study epidemiological study over 25 years: the Lundby Study. *Psychol Med*. 1982;12:279-289.

8. Loftis JM, Hauser P. The phenomenology and treatment of interferon-induced depression. *J Affect Disord*. 2004;82:175-190.
9. Asnis GM, De La Garza R, 2nd. Interferon-induced depression in chronic hepatitis C: a review of its prevalence, risk factors, biology, and treatment approaches. *J Clin Gastroenterol*. 2006;40:322-335.
10. Schaefer M, Engelbrecht MA, Gut O, et al. Interferon alpha (IFNalpha) and psychiatric syndromes: a review. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:731-746.
11. Trask PC, Esper P, Riba M, Redman B. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *J Clin Oncol*. 2000;18:2316-26.
12. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs*. 2005;19:105-123.
13. Reichenberg A, Gorman JM, Dieterich DT. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. *AIDS*. 2005;19:S174-S178.
14. Dieperink E, Ho SB, Thuras P, Willenbring ML. A prospective study of neuropsychiatric symptoms associated with interferon-a-2b and ribavirin therapy for patients with chronic hepatitis C. *Psychosomat*. 2003;44:104-112.

Pharmacological aspects

Depresión mayor durante el tratamiento con α-interferón: vulnerabilidad y prevención

El trastorno depresivo mayor (TDM) durante el tratamiento con α-interferón (αIFN) puede presentarse a los pocos meses de terapia y comparte muchas características con otras formas de TDM. La mayoría de los pacientes son resilientes al efecto lateral de la depresión inducida por interferón (TDM-IFN), pero el 15% a 40% es vulnerable. Varios estudios han utilizado antidepresivos para prevenir la incidencia de un episodio de TDM-INF y los resultados sugieren que los antidepresivos profilácticos pueden ser empleados específicamente en quienes tienen síntomas subumbrales pre-existentes y/o una historia de episodios previos de TDM. Se han propuesto varios potenciales marcadores de vulnerabilidad para el TDM-INF en la evaluación de pacientes no depresivos antes de iniciar el αINF. Estos incluyen una mala calidad del sueño, aumento premórbido de las citoquinas inflamatorias, polimorfismo genético en el sistema serotoninérgico, personalidad y apoyo social. El interjuego de estos factores predice en forma importante quién está en riesgo de un TDM-INF y señala varios blancos potencialmente modificables para una prevención personalizada del TDM-INF.

Dépression majeure au cours d'un traitement par interféron-α : vulnérabilité et prévention

Un épisode dépressif majeur (EDM) peut survenir au cours des premiers mois d'un traitement par interféron-α (IFN-α), montrant des similitudes avec les autres formes de dépression caractérisées. La plupart des patients présentent une résilience à cette dépression induite par l'interféron mais 15 à 40 % y sont vulnérables. Plusieurs études ayant utilisé des antidépresseurs pour prévenir la survenue d'un EDM lié à l'IFN (IFN-EDM) ont montré qu'une prophylaxie antidépressive peut être utilisée spécifiquement chez les patients ayant une symptomatologie dépressive infraclinique et/ou des antécédents d' EDM. Des patients non dépressifs ont été testés avec des marqueurs potentiels de susceptibilité aux IFN-EDM avant de débuter un traitement par IFN-α. Ils incluent un sommeil de mauvaise qualité, une augmentation prémorbide des cytokines inflammatoires, des polymorphismes génétiques du système sérotoninergique, des éléments de la personnalité et de l'environnement social. L'interaction de ces facteurs prédit fortement qui est à risque d'IFN-EDM et constitue certaines cibles potentiellement modifiables dans le cadre de la prévention personnalisée de l'IFN-EDM.

15. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry*. 2002;7:942-947.

16. Castera L, Constant A, Henry C, et al. Impact on adherence and sustained viological response of psychiatric side effects during peginterferon and ribavirin therapy for chronic hepatitis C. *Alimentary Pharmacol Therapeut*. 2006;24:1223-1230.

17. Schaefer M, Schmidt F, Horn M, Schmid-Wendtner M-H, Volkenandt M. Depression during treatment with interferon alpha. *Psychosomat*. 2004;45:176.

18. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-a: recognition and management. *CNS Drugs*. 2005;19:105-123.

19. Cotler SJ, Wartelle CF, Larson AM, Gretch DR, Jensen DM, Carithers RLJ. Pretreatment symptoms and dosing regimen predict side-effects of interferon therapy for hepatitis C. *J Viral Hepatitis*. 2000;7:211-217.

20. Dieperink E, Willenbring M Ho SB. Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: a review. *Am J Psychiatry*. 2000;157:867-876.

21. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Ferlito L, Rampello L. Interferon alpha-induced depression in chronic hepatitis C patients: Comparison between different types of interferon alpha. *Neuropsychobiol*. 1998;37:93-97.

22. Capuron L, Hauser P, Hinze-Selch D, Miller AH, Neveu PJ. Treatment of cytokine-induced depression. *Brain Behav Immunology*. 2002;16:575-580.

23. Donnelly S. Patient management strategies for interferon alfa-2b as adjuvant therapy of high-risk melanoma. *Oncologic Nursing Forum*. 1998;25:921-927.

24. Trask PC, Esper P, Riba M, Redman B. Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions. *J Clin Oncol*. 2000;18:2316-2326.

25. Pavol MA, Meyers CA, Rexer JL, Valentine AD, Mattis PJ, Talpaz M. Pattern of neurobehavioral deficits associated with interferon alfa therapy for leukemia. *Neurol*. 1995;45:947-950.

26. Malaguarnera M, Laurino A, Di Fazio I, et al. Neuropsychiatric effects and type of IFN-a in chronic hepatitis C. *J Interferon Cytokine Res*. 2001;21:273-278.

27. Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Int Med*. 1987;147:1577-1580.

28. Capuron L, Gumnick JF, Musselman DL, et al. Neurobehavioral effects of interferon-a in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacol*. 2002;26:643-652.

29. Hosoda S, Takimura H, Shibayama M, Kanamura H, Ikeda K, Kumada H. Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. *Psychiatry Clin Neurosci*. 2000;54:565-572.

30. Bonaccorso S, Marino V, Biondi M, Grimaldi F, Ippoliti F, Maes M. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J Affect Dis*. 2002;72:237-241.

31. Lin R, Roach E, Zimmerman M, Strasser S, Farrell GC Group) AHCS. Interferon alfa-2b for chronic hepatitis C: effects of dose increment and duration of treatment on response rates. *J Hepatol*. 1995;23:487-496.

32. Spath-Schwalbe E, Lange T, Perras B, Fehm HL, Born J. Interferon-alpha acutely impairs sleep in healthy humans. *Cytokine*. 2000;12:518-521.

33. Poutiainen E, Hokkanen L, Niemi M, Farkkila M. Reversible cognitive decline during high-dose [alpha]-interferon treatment. *Pharmacol Biochem Behav*. 1994;47:901-905.

34. Merimsky O, Reider-Groswasser I, Inbar M, Chaitchik S. Interferon-related mental deterioration and behavioral changes in patients with renal cell carcinoma. *Eur J Cancer*. 1990;26:596-600.

35. McHutchinson JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patents with chronic hepatitis C. *Gastroenterol*. 2002;122:1061-1069.

36. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. *Hepatol*. 1997;26:112S-121S.

37. Fontana RJ, Schwartz SM, Gebremariam A, Lok ASF, Moyer CA. Emotional distress during interferon-a-2B and ribavirin treatment of chronic hepatitis C. *Psychosomat*. 2002;34:378-385.

38. Janssen H, Brouwer J, van der Mast R, Schalm S. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol*. 1994;21:241-243.

39. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med*. 1998;339:1485-1492.

40. Enns MW, Cox BJ. Personality dimensions and depression: review and commentary. *Can J Psychiatry - Revue Canadienne de Psychiatrie.* 1997;42:274-284.

41. Boyce P, Mason C. An overview of depression-prone personality traits and the role of interpersonal sensitivity. *Austr New Zealand J Psychiatry*. 1996;30:90-103.

42. Joiner TE. Depression in its interpersonal context. In: Gotlieb IH, Hammen CL, eds. *Handbook of Depression*. New York, NY: Guilford; 2002:295-313.

43. Fabrega HJ. *Disease and Social Behavior: an Interdisciplinary Perspective*. Cambridge, MA: MIT Press; 1974.

44. Mullen L, S, Blanco C, Vaughan SC, Vaughan R, Roose SP. Defense mechanisms and personality in depression. *Depress Anx*. 1999;10:168-174.

45. Gilbert P. Evolutionary approaches to psychopathology: the role of natural defences. *Aust N Z J Psychiatry*. 2001;35:17-27.

46. Parker G, Lipscombe P. The relevance of early parental experiences to adult dependency, hypochondriasis and utilization of primary physicians. *Br J Med Psychol*. 1980;53:355-363.

47. Granek M. Hypochondriasis, acting out and counter-acting out. *Br J Med Psychol*. 1989;62:257-264.

48. Hofmann AD. The impact of illness in adolescence and coping behavior. *Acta Paediatrica Scand (Supplement).* 1975;256:29-33.

49. Scheurich N. Hysteria and the medical narrative. *Persp Biol Med*. 2000;43:461-476.

50. Kihlstrom JF, Cantor Kihlstrom L. Somatization as illness behavior. *Adv Mind-Body Med*. 2001;17:240-243.

51. Maes M. Psychological stress, cytokines, and the inflammatory response system. *Curr Opin Psychiatry*. 1999;12:695-700.

52. Schwarz MJ, Chiang S, Muller N, Ackenheil M. T-Helper-1 and T-helper-2 responses in psychiatric disorders. *Br Behav Immunol*. 2001;15:340-370.

53. Vollmer-Conna U. Acute sickness behavior: an immune system-to-brain communication? *Psychol Med*. 2001;31:761-767.

54. Miller GE, Rohleder N, Stetler C, et al. Clinical depression and regulation of the inflammatory response during acute stress. *Psychosomat Med*. 2005;67:679-687.

55. Pace TW, Mletzko TC, Alagbe O, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry*. 2006;163:1630-1633.

56. Morikawa O, Sakai N, Obara H, Saito N. Effects of interferon-alpha, interferon-gamma and cAMP on the transcriptional regulation of the serotonin transporter. *Eur J Pharmacol*. 1998;349:317-324.

57. Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-[alpha]-based immunotherapy are related to interferon-[alpha]-induced changes in the serotonergic system. *J Clin Psychopharmacol*. 2002;22:86-90.

58. Rosel P, Arranz B, Vallejo J, et al. Altered [3H]imipramine and 5-HT2 but not [3H]paroxetine binding sites in platelets from depressed patients. *J Affect Dis*. 1999;52:225-233.

59. Neumeister A, Konstantinidis A, Stastny J, et al. Association between serotonin transporter gene promoter polymorphism (5HTTLPR) and behavioral responses to tryptophan depletion in healthy women with and without family history of depression. *Arch Gen Psychiatry*. 2002;59:613-620.

60. Shuto H, Kataoka Y, Horikawa T, Fujihara N, Oishi R. Repeated interferon-a administration inhibits dopaminergic neural activity in the mouse brain. *Br Res*. 1997;747:348-351.

61. Song C, Merali Z, Anisman H. Variations of nucleus accumbens dopamine and serotonin following systemic interfleukin-1, interleukin-2, or interleukin-6 treatment. *Neurosci*. 1999;88:823-836.

62. Hanisch U-K, Quirion R. Interleukin-2 as a neuroregulatory cytokine. *Br Re Rev*. 1996;21:246-284.

63. Song C, Lin A, Bonaccorso S, et al. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *J Affect Dis*. 1998;49:211-219.

64. Katafuchi T, Kondo T, Yasaka T, Kubo K, Take S, Yoshimura M. Prolonged effects of polyriboinosinic:polyribocytidylic acid on spontaneous running wheel activity and brain interferon-alpha mRNA in rats: a model for immunologically induced fatigue. *Neurosci*. 2003;120:837-845.

65. Licinio J, Wong M-L. Pathways and mechanisms for cytokine signaling of the central nervous system. *J Clin Invest*. 1997;100:2941-2947.

66. Hansen MK, Taishi P, Chen Z, Krueger JM. Vagotomy blocks the induction of interleukin-1b (IL-1b) mRNA in the brain of rats in response to systemic IL-1b. *J Neurosci*. 1998;18:2247-2253.

67. Yirmiya R, Pollak Y, Baak O, et al. Effects of antidepressant drugs on the behavioral and physiological responses to lipopolysaccharide (LPS) in rodents. *Neuropsychopharmacol*. 2001;24:531-544.

68. Anisman H, Kokkinidis L, Merali Z. Further evidence for the depressive effects of cytokines: Anhedonia and neurochemical changes. *Br Behav Immunol*. 2002;16:544-556.

69. Larson SJ. Behavioral and motivational effects of immune-system activation. *J Gene Psychol*. 2002;129:401-414.

70. Larson SJ, Dunn AJ. Behavioral effects of cytokines. *Br Behav Immun*. 2001;15:371-387.

71. Dantzer R, Aubert A, Bluthe R-M, et al. Mechanisms of the behavioral effects of cytokines. *Adv Exp Med Biol*. 1999;461:83-106.

72. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Br Behav Immun*. 2007;21:153-160.

73. Maier SF, Nguyen KT, Deak T, Milligan ED, Watkins LR. Stress, learned helplessness, and brain interleukin-1b. *Adv Exp Med Biol*. 1999;461:235-250.

74. Makino M, Kitano Y, Komiyama C, Hirohashi M, Takasuna K. Involvement of central opioid systems in human interferon-a induced immobility in the mouse forced swimming test. *Br J Pharmacol*. 2000;130:1269-1274.

75. Makino M, Kitano Y, Komiyama C, Takasuna K. Human interferon-a increases immobility in the forced swimming test in rats. *Psychopharmacol*. 2000;148:106-110.

76. Schramm TM, Lawford BR, Macdonald GA, Cooksley WG. Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust*. 2000;173:359-361.

77. Gleason OC, Yates WR. Five cases of interferon-a-induced depression treated with antidepressant therapy. *Psychosomat*. 1999;40:510-512.

78. Gleason OC, Yates WR, Isbell MD, Philipsen MA. An open-label trial of citalopram for major depression in patients with hepatitis C. *J Clin Psychiatry*. 2002;63:194-198.

79. Kraus MR, Schafer A, Schottker K, et al. Therapy of interferon-induced depression in chronic hepatitis C with citalopram: a randomized, double-blind, placebo-controlled study. *Gut*. 2008;57:531-536.

80. Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;344:961-966.

81. Goldman LS. Successful treatment of interferon-a-induced mood disorders with nortriptyline. *Psychosomat*. 1994;35:412-413.

82. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon-a. *Am J Gastroenterol*. 1993;88:760-761.

83. Hauser P, Soler R, Reed S, et al. Prophylactic treatment of depression induced by interferon-a. *Psychosomat*. 2000;41:439-442.

84. Farah A. Interferon-induced depression treated with citalopram. *J Clin Psychiatry*. 2002;63:166-167.

85. Morasco BJ, Rifai MA, Loftis JM, Indest DW, Moles JK, Hauser P. A randomized trial of paroxetine to prevent interferon-a-induced depression in patients with hepatitis C. *J Affect Dis.* 2007;103:83-90.

86. Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *Gen Hosp Psychiatry.* 2003;25:34-38.

87. Hauser P, Khosla J, Aurora H, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. *Mol Psychiatry*. 2002;7:942-947.

88. Juengling FD, Ebert D, Gut O, et al. Prefrontal cortical hypometabolism during low-dose inteferon alpha treatment. *Psychopharmacol*. 2001;152:383-389.

89. Capuron L, Pagnoni G, Demetrashvili M, et al. Anterior cingulate activation and error processing during interferon-alpha treatment. *Biol Psychiatry*. 2005;58:190-196.

90. Abe S, Hori T, Suzuki T, Baba A, Shiraishi H, Yamamoto T. Effects of chronic administration of interferon alpha A/D on serotonergic receptors in rat brain. *Neurochemic Res*. 1999;24:359-363.

91. Capuron L, Neurauter G, Musselman DL, et al. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biol Psychiatry*. 2003;54:906-914.

92. Dunn AL, Crnic LS. Repeated injections of interferon-alpha A/D in Balb/c mice: behavioral effects. *Brain Behav Immun*. 1993;7:104-111.

93. Wichers MC, Maes M. The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon-alpha-induced depression. *J Psychiatry Neurosci*. 2004;29:11-17.

94. Chou R, Clark EC, Helfand M. Screening for Hepatitis C virus infection: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Int Med*. 2004;140:465-479.

95. Baron S, Tyring SK, Fleischmann WR. The interferons: mechanisms of action and clinical applications. *JAMA*. 1991;266:1375-1383.

96. Borden EC, Parkinson D. A perspective on the clinical effectiveness and tolerance of interferon-(alpha). *Sem Oncol*. 1998;25:3-8.

97. Memon MI, Memon MA. Hepatitis C: an epidemiological review. *J Viral Hepatitis.* 2002;9:84-100.

98. Williams I. Epidemiology of hepatitis C in the United States. *Am J Med*. 1999;107:2S-9S.

99. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *Centers for Disease Control and Prevention, MMWR Recomm Rep*. 1998;47:1-39.

100. Zdilar D, Franco-Bronson K, Buchler N, Locala JA, Younossi ZM. Hepatitis C, interferon alfa, and depression. *Hepatol*. 2000;31:1207-1211.

101. Castera L, Constant A, Henry C, Couzigou P. Psychiatric disorders during treatment of chronic hepatitis C. *Gastroenterol Clin Biol*. 2005;29:123-133.

102. Dan AA, Martin LMC, Ong JP, et al. Depression, anemia and health-related qulity of life in chronic hepatitis C. *J Hepatol*. 2006;44:491-498.

103. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatol*. 2007;45:806-816.

104. Gleason OC, Fucci JC, Yates WR, Philipsen MA. Preventing relapse of major depression during interferon-a therapy for hepatitis C - a pilot study. *Dig Dis Sci*. 2007;52:2557-2563.

105. Kraus MR, Schafer A, Scheurlen M. Paroxetine for the prevention of depression induced by interferon alfa. *N Engl J Med*. 2001;345:375-376.

106. Raison CL, Woolwine BJ, Demetrashvili ZM, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Alimentary Pharmacol Therapeut*. 2007;25:1163-1174.

107. Schaefer M, Schwaiger M, Garkish AS, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol*. 2005;42:793-798.

108. Cuijpers P, Smit F, Straten A. Psychological treatment of subthreshold depression: a systematic review. *Acta Psychiatrica Scand*. 2007;115:434-441.

109. Rovner BW, Casten RJ. Preventing late-life depression in age-related macular degeneration. *Am J Geriatr Psychiatry*. 2008;16:454-459.

110. Munoz RF, Le HL, Ghosh-Ippen C, Diaz MA, Urizar GG, Soto J. Prevention of postpartum depression in low-income women: Development of the mams y bebs/mothers and babies course. *Cog Behav Practice*. 2007;14:70-83.

111. Schoevers RA, Smit F, Deeg DJH, et al. Prevention of late-life depression in primary care: do we know where to begin? *Am J Psychiatry*. 2006;163:1611-1621.

112. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alfa therapy by the patients initial affective state. *N Engl J Med*. 1999;340:1370.

113. Raison CL, Borisov AS, Broadwell SD, et al. Depression during pegylated interferon-alpha plus ribarin therapy: prevalence and prediction. *J Clin Psychiatry*. 2005;66:41-48.

114. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry*. 2009;65:344-348.

115. Lotrich FE, Rabinovitz F, Gironda P, Pollock BG. Depression following pegylated interferon-alpha: characteristics and vulnerability. *J Psychosomat Res*. 2007;63:131-135.

116. Frank E, Kupfer DJ, Perel JM, Cornes C, Jarret DB, Mallinger AG. Three-year outcomes for maintenance therapies in recurrent depression. *Arch Gen Psychiatry.* 1990;47:1093-1099.

117. Geddes JR, Carney SM, Davies CH, Furukawa TA, Kupfer DJ. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*. 2003;361:653-661.

118. Klein DN, Santiago NJ, Vivian D, Arnow BA, Blalock JA, Dunner DL. Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. *J Consul Clin Psychol*. 2004;72:681-688.

119. Fava GA, Ruini C, Rafanelli C, Finos L, Conti S, Grandi S. Six-year outcome of cognitive behavior therapy for prevention of recurrent depression. *Arch Gen Psychiatry*. 2004;161:1872-1876.

120. Kraus MR, Shafer A, Al-Taie O, Scheurlen M. Prophylactic SSRI during interferon alpha re-therapy in patients with chronic hepatitis C and a history of interferon-induced depression. *J Viral Hepatitis*. 2006;12:96-100.

121. Capuron L, Ravaud A, Miller AH, Dantzer R. Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. *Br Behav Immunol*. 2004;18:205-213.

122. Franzen PL, Buysse DJ, Rabinovitz M, Pollock BG, Lotrich FE. Poor sleep quality predicts onset of either major depression or subsyndromal depression with irritability during interferon-alpha treatment. *Psychiatric Research*. 2009. In press.

123. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatric Research*. 1989;28:193-213.

124. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262:1479-1484.

125. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39:411-418.

126. Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? *J Affect Disord*. 2003;76:255-259.

127. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study. *Am J Epidemiol*. 1997;146:105-114.

127. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262:1479-1484.

129. Horikawa N, Yamazaki T, Izumi N, Uchihara M. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *Gen Hosp Psychiatry*. 2003;25:34-38.

130. Miyaoka H, Otsubo T, Kamijima K, Ishii M, Onuki M, Mitamura K. Depression from interferon therapy in patients with hepatitis C. *Am J Psychiatry*. 1999;156:1120.

131. Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J Clin Psychiatry*. 2003;64:708-714.

132. Wichers MC, Kenis G, Leue C, Koek G, Robaeys G, Maes M. Baseline immune activation as a risk factor for the onset of depression during interferon-alpha treatment. *Biol Psychiatry*. 2006;60:77-79.

133. Prather AA, Rabinovitz M, Pollock BG, Lotrich FE. Cytokine-induced depression during IFN-α treatment: the role of IL-6 and sleep quality. *Brain Behav Immun*. 2009;23:1109-1116.

134. Bull SJ, Huezo-Diaz P, Binder EB, et al. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-a and ribavirin treatment. *Mol Psychiatry*. 2008;14:1-10.

135. Pike JL, Irwin MR. Dissociation of inflammatory markers and natural killer cell activity in major depressive disorder. *Br Behav Immun*. 2006;20:169-174.

136. Maes M, Meltzer HY, Bosmans E, et al. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *J Affect Disord*. 1995;34:301-309.

137. Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:228-233.

138. Sluzewska A, Rybakowski J, Bosmans E, et al. Indicators of immune activation in major depression. *Psychiatry Res*. 1996;64:161-167.

139. Musselman DL, Miller AH, Porter MR, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. *Am J Psychiatry*. 2001;158:1252-1257.

140. Dimopoulos N, Piperi C, Psarra V, Lea RW, Kalofoutis A. Increased plasma levels of 8-iso-PGF2alpha and IL-6 in an elderly population with depression. *Psychiatry Res*. 2008;161:59-66.

141. Mariani E, Neri S, Cattini L, et al. Effect of zinc supplementation on plasma IL-6 and MCP-1 production and NK cell function in healthy elderly: interactive influence of +647 MT1a and -174 IL-6 polymorphic alleles. *Exp Gerontol*. 2008;43:462-471.

142. Nicklas BJ, Hsu F-C, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc*. 2008;56:2045-2052.

143. Lambert CP, Wright NR, Finck BN, Villareal DT. Exercise but not diet-induced weight loss decreases skeletal muscle inflammatory gene expression in frail obese elderly persons. *J App Physiol*. 2008;105:473-478.

144. McDonald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity: an investigation in a trial of recombinant a-interferon in hepatitis-B carriers. *Lancet*. 1987;II:1175-1178.

145. Otsubo T, Miyaoka H, Kamijima K, Onuki M, Ishii M, Mitamura K. Depression during interferon therapy in chronic hepatitis C patients - a prospective study. *Seishin Shinkeigaku Zasshi (Jpn)*. 1997;99:101-127.

146. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry*. 2009;65:344-348.

147. Capuron L, Raison CL, Musselman DL, Lawson DH, Nemeroff CB, Miller AH. Association of exaggerated HPA axis response to the initial injection of interferon-alpha with development of depression during interferon-alpha treatment. *Am J Psychiatry*. 2003;160:1342-1345.

148. Pace TWW, Hu F, Miller AH. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Br Behav Immun*. 2007;21:9-19.

149. Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry*. 2001;49:391-404.

150. Antonijevic I. HPA axis and sleep: identifying subtypes of major depression. *Stress*. 2008;11:15-27.

151. Heydendael W, Jacobson L. Differential effects of imipramine and phenelzine on corticosteroid receptor gene expression in mouse brain: potential relevance to antidepressant response. *Brain Res*. 2008;1238:93-107.

152. Carvalho LA, Pariante CM. In vitro modulation of the glucocorticoid receptor by antidepressants. *Stress*. 2008;11:411-424.

153. Simon NG, Guillon C, Fabio K, et al. Vasopressin antagonists as anxiolytics and antidepressants: recent developments. *Recent Patents on CNS Drug Discovery*. 2008;3:77-93.

154. Aihara M, Ida I, Yuuki N, et al. HPA axis dysfunction in unmedicated major depressive disorder and its normalization by pharmacotherapy correlates with alteration of neural activity in prefrontal cortex and limbic/paralimbic regions. *Psychiatry Res*. 2007;155:245-256.

155. Kraus MR, Al-Taie O, Schefer A, Pfersdorff M, Lesch KP, Scheurlen M. Serotonin-1A receptor gene (HTR1A) variation predicts interferon-induced depression chronic hepatitis C. *Gastroenterol*. 2007;132:1279-1286.

156. Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol Psychiatry*. 2002;7:468-473.

157. Gohier B, Goeb JL, Rannou-Dubas K, Fouchard I, Cales P, Garre JB. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World J Biol Psychiatry*. 2003;4:115-118.

158. Koskinas J, Merkouraki P, Manesis E, Hadziyannis S. Assessment of depression in patients with chronic hepatitis: effect of interferon treatment. *Dig Dis Sci*. 2002;20:284-288.

159. Smits F, Smits N, Schoevers R, Deeg D, Beekman A, Cuijpers P. An epidemiological approach to depression prevention in old age. *Am J Geriatr Psychiatry*. 2008;16:444-453.

160. Cole MG. Evidence-based review of risk factors for geriatric depression and brief preventative interventions. *Psychiatr Clin N Am*. 2005;28:785-803.

161. Brodaty H, Green AA, Koschera A. Meta-analysis of psychosocial interventions for caregivers of people with dementia. *J Am Geriatr Soc*. 2003;51:657-664.

162. Forster A, Young J. Specialist nurse support for patients with stroke in the community: a randomized controlled trial. *BMJ*. 1996;312:1642-1646.

163. Narushima K, Kosier TJ, Robinson RG. Preventing poststroke depression: a 12-week double blind randomized treatment trial and 21-month follow-up. *J Nerv Ment Dis*. 2002;190:296-303.

164. Rasmussen BB, Lunde M, Loldrup PD, et al. A double-blind placebo-controlled study of sertraline in the prevention of depression in stroke patients. *Psychosomatics*. 2003;44:216-221.

165. Austin MP. Targeted group antenatal prevention of postnatal depression: a review. *Acta Psychiatrica Scand*. 2003;107:2444-2250.

166. Dennis CLE. Preventing postpartum depression Part II: a critical view of nonbiological interventions. *Can J Psychiatry*. 2004;49:526-538.

167. Cole MG. Brief interventions to prevent depression in older subjects: a systematic review ofe feasibility and effectiveness. *Am J Geriatr Psychiatry*. 2008;16:435-443.

168. Barrera AZ, Torres LD, Munoz RF. Prevention of depression: the state of the science at the beginning of the 21st century. *Int Rev Psychiatry*. 2008;19:655-670.