Major Depressive Disorder (MDD) is common, costly,

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%. 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—

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.

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 non-depressed 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.
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.

MDD during IFN-α treatment (IFN-MDD) typically develops within the first 2 or 3 months of administration, and occurs in about 15% to 40% of patients. 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, studies with control groups, and prospective documentations of worsening depression during IFN-α treatment with a return to baseline mood after discontinuation. Thus, IFN-MDD is a replicable finding in prospective studies. Second, IFN-MDD has phenomenological resemblance to MDD diagnosed in other situations. 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.

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.
- Psychosocial stress can increase the levels of inflammatory cytokines.
- IFN-α and other cytokines can affect central monoaminergic systems plausibly involved in MDD.
- Peripheral cytokines and IFN-α have access to the CNS through a variety of routes in addition to being synthesized in the brain.
- Endogenous IFN-α mRNA can be induced in the cortex, hippocampus, and hypothalamus, with correlated changes in behavior in animal models of depression.
- Systemic administration of IFN-α and other cytokines can affect amotivation and anhedonia behaviors in rodent models of depression.
- 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, with about 79% to 85% of patients responding to antidepressants.
- IFN-α administration can influence frontal lobe and anterior cingulate function, dopaminergic activity, and serotonergic function—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), whereas about 170 million people worldwide have been infected with HCV. Supporting IFN-α's widespread use, untreated chronic HCV can lead to cirrhosis, hepatocellular cancer, and liver failure.
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).\textsuperscript{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.\textsuperscript{86} Similarly, in three open-label trials of prophylactic SSRIs given to nondepressed HCV patients, only 3/32 patients (9%) developed IFN-MDD, as compared with 25% of untreated patients.\textsuperscript{86} 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.\textsuperscript{84,85} 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.\textsuperscript{88} 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.\textsuperscript{88} This would be an example of “indicated prevention” whereby treating “subthreshold” depression symptoms may prevent subsequent worsening to full categorical MDD.\textsuperscript{108-111} It has been well-replicated that higher levels of pretreatment depression symptoms are associated with the development of IFN-MDD,\textsuperscript{108,112-117} 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.\textsuperscript{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 developed IFN-MDD, while 47.6% (10/21) not on antidepressants developed IFN-MDD. 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 | RCT 18 vs 20     | Melanoma patients; average HAM-D>5 | DSM-IV     | Prevented IFN-MDD, 2/18 vs 9/20 |
| Paroxetine | RCT 14 vs 19     | Average HAM-D<3           | DSM-IV     | Did not prevent IFN-MDD, 5/14 vs 6/19 |
| Paroxetine | RCT 23 vs 29     | Median MADRS = 3          | DSM-IV or MADRS>15 | Did not prevent IFN-MDD, 3/23 vs 6/29 |
| Citalopram | Open label 10 vs 0 | MDD history in remission | HAM-D = 17 | Benefit for patients with baseline MADRS >3 |
| Paroxetine or Citalopram | 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 |
| Citalopram | 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 (DSM-IV), the Hamilton Depression rating scale (HAM-D), or the Montgomery-Asberg Depression Rating Scale (MADRS).
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more targeted use of SSRIs to prevent recurrence, limiting prophylactic SSRIs 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, χ²=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 (χ²=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%,138,110 or with studies preventing recurrence of MDD.114-119 A more targeted prevention RCT would be valuable to examine these two possibilities; (iii) Even if SSRIs are found to be effective prophylactically for some people, about 15% to 20% of patients still develop 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.121,139 Patients with scores greater than 10 on the Pittsburgh Sleep Quality Index, a validated self-report assessment of sleep quality,15 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.135 This is consistent with cross-sectional studies in which elevated IL-6 levels are associated with MDD.136-140 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 diet141 and/or exercise.142,143 Potential premorbid risk factors for IFN-MDD that may be modifiable through psychosocial interventions could include social isolation144 and neuroticism.145,146 However, when controlling for other premorbid risk factors, the effect size for these is fairly small.147 Another risk factor may be a hyperactive stress response in the hypothalamic-pituitary-adrenal (HPA) axis.148 Given the common association between abnormalities in the HPA axis and MDD,149-150 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 therapy147—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. Two studies have replicated the finding that a short allele in the serotonin transporter robustly increases risk for IFN-MDD. Vulnerability to tryptophan depletion has also been associated with polymorphisms in the 5-HT reuptake transporter. Because IFN-MDD has been associated with lowered tryptophan levels during treatment, 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, 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 abstenent, a past history of drug and alcohol abuse is not predictive of increased risk. 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 transferable to other types of MDD. As examples, MDD occurs at higher rates in populations with multiple chronic illnesses, during bereavement, in caregivers of demented patients, in stroke survivors, in post-partum mothers, and there is preliminary evidence that MDD incidence could potentially be reduced in these settings. Similar to IFN-MDD, most people in these settings are resilient to developing MDD, with only a subset who are vulnerable.

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.

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#### 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-IFN 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 ha propuesto varios potenciales marcadores de vulnerabilidad para el TDM-IFN en la evaluación de pacientes no depresivos antes de iniciar el αIFN. Estos incluyen una mala calidad del sueño, aumento pre-morbídeo 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-IFN y señala varios blancos potencialmente modificables para una prevención personalizada del TDM-IFN.

#### 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 prédisait 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.

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