Fatigue is an extremely common symptom with many possible causes. New medications have been introduced which treat multiple causes of fatigue effectively, raising awareness and manageability of the condition.

I. Fatigue as a ‘sixth sense’
   a. Physical effort
   b. Mental effort

II. Excessive sleepiness
   a. Increased sleep drive
   b. Sleep disruption
   c. Circadian misalignment
   d. Accumulated sleep debt
   e. Functional impairment
      i. Impact on activities of daily living
      ii. Decreased concentration
      iii. Makes concomitant conditions worse, e.g., diabetic control

III. Diagnostic workup
   a. History
      i. Frequency of fatigue or sleepiness
      ii. Degree of impairment
      iii. Situational contributors
      iv. Epworth Sleepiness Scale
   b. Differential Diagnosis
      i. Narcolepsy
         1. Irresistible sleep attacks
         2. Cataplexy
         3. Hypnagogic hallucinations
         4. Sleep paralysis
         5. Disrupted night time sleep
      ii. Idiopathic hypersomnolence
         1. Neurogenic fatigue
         2. Fatigue related to multiple sclerosis
         3. Fatigue related to Binswanger’s disease
      iii. Sleep-disordered breathing
         1. Obstructive sleep apnea syndrome
2. Upper airway resistance syndrome
   iv. Sleep-movement disorders
      1. Periodic limb movements of sleep
      2. REM behavior disorder
c. Physical examination
d. Neurological examination
e. Laboratories
   i. Polysomnography
   ii. Actigraphy
   iii. For narcolepsy
      1. Decreased hypocretin levels in CSF
      2. Positive HLA-DR2

IV. Pharmacological Therapy of Fatigue

a. Stimulants
   i. Methylphenidate (Ritalin, et al.)
   ii. Dextroamphetamine (Dexedrine)
   iii. Mixed amphetamine salts (Adderall, Adderall XR)
   iv. Pemoline (Cylert) – watch for hepatotoxicity!
   v. Amantadine (Symmetrel) – nausea, sleep disruption
   vi. Venlafaxine (Effexor XR) – avoid plain or generic Effexor

b. Modafinil (Provigil)
   i. Not a stimulant, works specifically in the hypothalamus and prefrontal cortex
   ii. Approved for narcolepsy
   iii. Approved for obstructive sleep apnea
   iv. Approved for shift work sleep disorder
   v. Dosing up to 1000 mg daily in divided doses is effective and safe.