State of the Science on Cancer-Related Fatigue (CRF): Measurement & Management: Where is the Evidence & Where are the Gaps?

Barbara F. Piper, DNSc, RN, AOCN, FAAN
Professor & Chair of Nursing Research
Scottsdale Healthcare/University of Arizona
Email: bpiper@shc.org;
bpiper@nursing.arizona.edu

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CRF: Where's the Evidence & Where are the Gaps?

- Significance
- Prevalence
- Definitions
  - National Comprehensive Cancer Network (NCCN)
  - Descriptors
  - Case Definitions
  - Syndrome Criteria
  - Phenotypes

CRF: Where's the Evidence & Where are the Gaps?

- Underlying Mechanisms
- Measurement
- Assessment & Management
  - Education
  - Provider & patient/family
    NCCN CRF Evidence-Based Guidelines
    - Barriers
    - Preliminary findings

CRF: Where's the Evidence & Where are the Gaps?

- Current disease & treatment status
- Differential Diagnosis
- The "Gang of & 7"
  - Anemia, comorbidity, activity level/deconditioning, emotional distress, nutrition, pain including symptom clusters, burden, & cognition problems
- Summary & future directions

CRF Significance

- **Frequency & Distress:**
  - One of the most frequent symptoms experienced;
  - More distressing than pain, nausea, vomiting;
    - Most likely because it affects all QOL domains:
    - Physical functioning
    - Ability to engage in activities that give meaning & value to life;
  - Remains under-reported, under-diagnosed, & under-treated.
- **Gaps:**
  - Can have negative effects on patient & family employment & financial status;
  - May be dose-limiting;*
  - May compromise timing & frequency of treatments;*
  - May affect treatment adherence;*
  - May affect survival.*

Barsevick, 2007; Berger et al., 2009; Hofman et al., 2007; Mormont et al., 2007; NIH Consensus Conference, 2003; Volgelzang et al., 1997. * = Medical & Nursing Studies

CRF: What do we know about it?

- Differs significantly & consistently:
  - From usual tiredness & from what healthy people experience
- Frequently precedes and/or accompanies
  - Most major illnesses;
- All age groups affected;
- Seldom occurs by itself
  - Frequently "clusters" with other Sx (i.e., pain, depression, insomnia)…but does it?
- Underlying mechanisms unknown

Barsevick, 2007; Berger et al., 2009; NIH Consensus Conference, 2003.

CRF Prevalence Rates

- **Chemotherapy:**
  - 80-90%
  - Pattern may depend on type of agent, route of administration, frequency of cycles;
  - Roller-coaster pattern Q3-4 wk cycles in early stage breast cancer;
  - One dose-dense study only:
    - Differs only on 1st of 2 consecutive cycles;
  - More longitudinal & comparative studies needed;
  - Studies also needed for weekly dosing & combination Rx.

Berger, 1998; Berger & Mitchell, 2008; Mitchell & Berger, 2008;

CRF Prevalence Rates

- **Oral targeted agents:**
  - Lack patient-reported outcome data (PROs)
  - Provider dependence on CTCAE
    - Developed by consensus;
    - Never psychometrically validated;
  - **One comparative study:**
    - Patient & MD agreement higher for more "objective", observable Sx than for the more "subtle" Sx such as CRF

Basch et al., 2006; Edgerly & Fojo, 2008.

CRF Prevalence Rates

- **Oral targeted agents:**
  - & different from existing CT profiles;
  - No comparative studies yet;
  - Orally-administered vs IV administered;
  - Longer treatment courses over time;
  - Difficult to compare CRF patterns across phase 1 & 2 drug trials
    - Small, heterogeneous samples

Basch et al., 2006; Edgerly & Fojo, 2008.

CRF Prevalence Rates

- **Radiation Therapy**
  - Almost universal (70-100%);
  - Cumulative over time
    - Peaks at 4-6 wks; then gradually declines over time
  - Patients feel worse not better
    - May think that Rx is not working; that disease is getting worse
    - Need to forewarn patients about this pattern

CRF Prevalence Rates

- **Radiation Therapy**
  - Most studies have been with external beam RT (EBT/teletherapy)
  - Limited data on other different types of RT
  - 3D conformal, Intensity modulated (IMRT), implant or brachytherapy
  - Gamma knife Rx
  - Localized/palliative care
  - Despite a few studies indicating cytokine release from the periphery affecting CNS release.

CRF Prevalence Rates

- **Surgery**
  - Very few studies in hospitalized patients;
  - Fewer in surgical patients;
  - One study reported increased CRF with longer hospitalization.
  - Few studies pre diagnosis/workup phases
  - Despite several studies indicating that
    - Baseline pretreatment CRF levels predict CRF levels over time.

CRF Prevalence Rates

- **Hormonal Therapy**
  - Not well-studied
  - Perhaps due to less frequent follow up & surveillance
  - In men with prostate cancer treated with hormone ablation
    - 14% (N=58) had severe CRF at baseline; 66% (N=38/58) three months later.

CRF Prevalence Rates

- **Biotherapy**
  - 70% report CRF with interferon
- **Combination Therapy**
  - Cross-sectional studies suggest increased CRF but more longitudinal studies are needed

CRF Prevalence Rates

- Type & stage of malignancy
  - Few comparative studies;
  - More known about early stage breast cancer patients than other tumor types:
    - Colorectal, lung, prostate, pancreatic, skin, brain etc
    - Hematologic & hereditary forms of cancer
  - One systematic review documented increased CRF in:
    - Lung cancer patients
    - Women with ovarian cancer, compared to their breast cancer counterparts

CRF Prevalence Rates

- **Advanced Disease:**
  - One systematic review in patients with incurable cancer:
  - Last 2 wks of life studies (Group 2)(88%) vs All other studies (Group 1)(74%)
  - CRF was the most prevalent Sx in both groups

CRF Prevalence Rates

- **Settings:**
  - Most are outpatient
  - Less known about inpatients, home care or palliative care/hospice patients
- **Costs:**
  - Employment, financial status, home help, caregiver/spouse/partner

CRF Prevalence Rates

- **Comorbidities:**
  - More studies are needed with specific types & their associated medications
  - A few studies report increased CRF with increasing numbers of comorbidities;

CRF Prevalence Rates

Demographics:

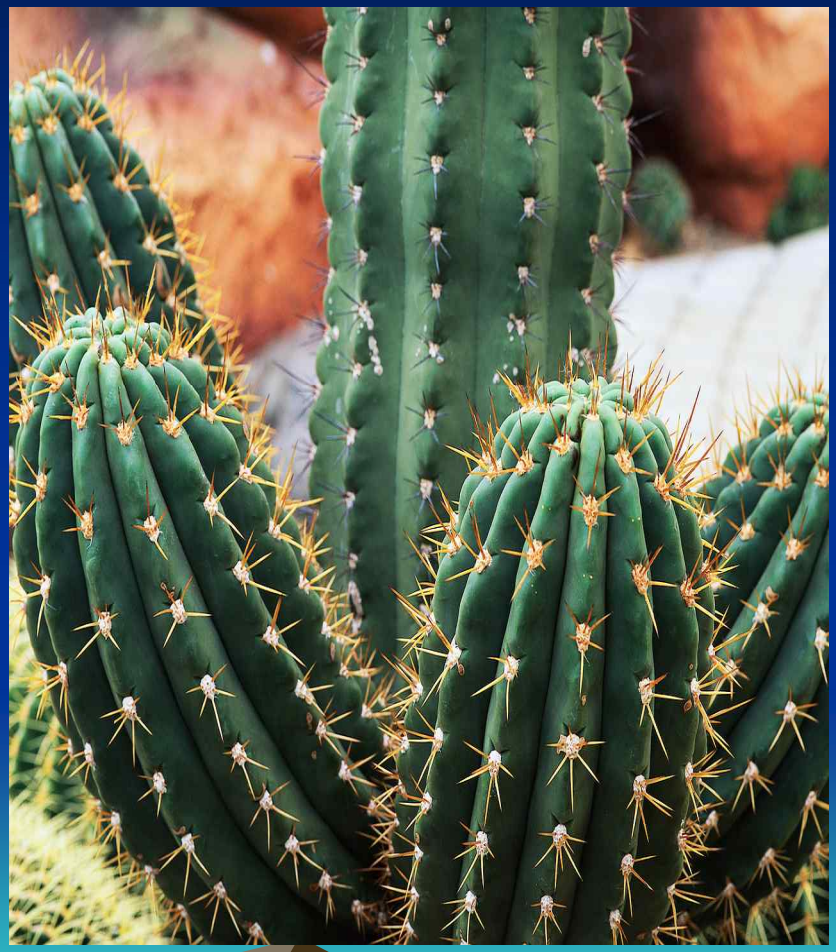
- One systematic review showed conflicting results
- Perhaps because the review did not control for the designs of studies (i.e., cross-sectional vs longitudinal)
- Findings suggest that women > than men; younger > than older

CRF Definitions

- Subjective perception
- Most commonly used definition: NCCN CRF Guidelines (www.nccn.org)
  - Distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness/exhaustion
  - Related to cancer or cancer treatment
  - Not proportional to recent activity
  - Interferes with usual functioning

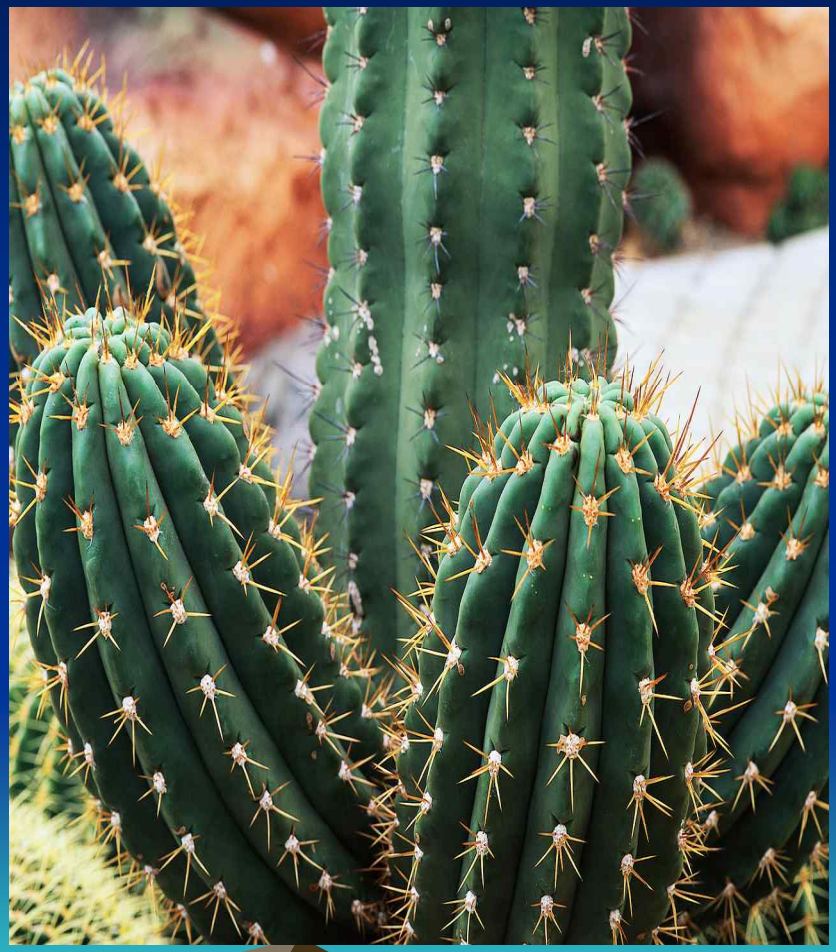
CRF Definitions

- **NCCN CRF Definition:**
  - Misses distinction from fatigue in healthy people
  - Misses disproportionate to patient's degree of exertion
- **Descriptors:**
  - More study needed as to how CRF manifestations or descriptors
    - Vary by culture & language



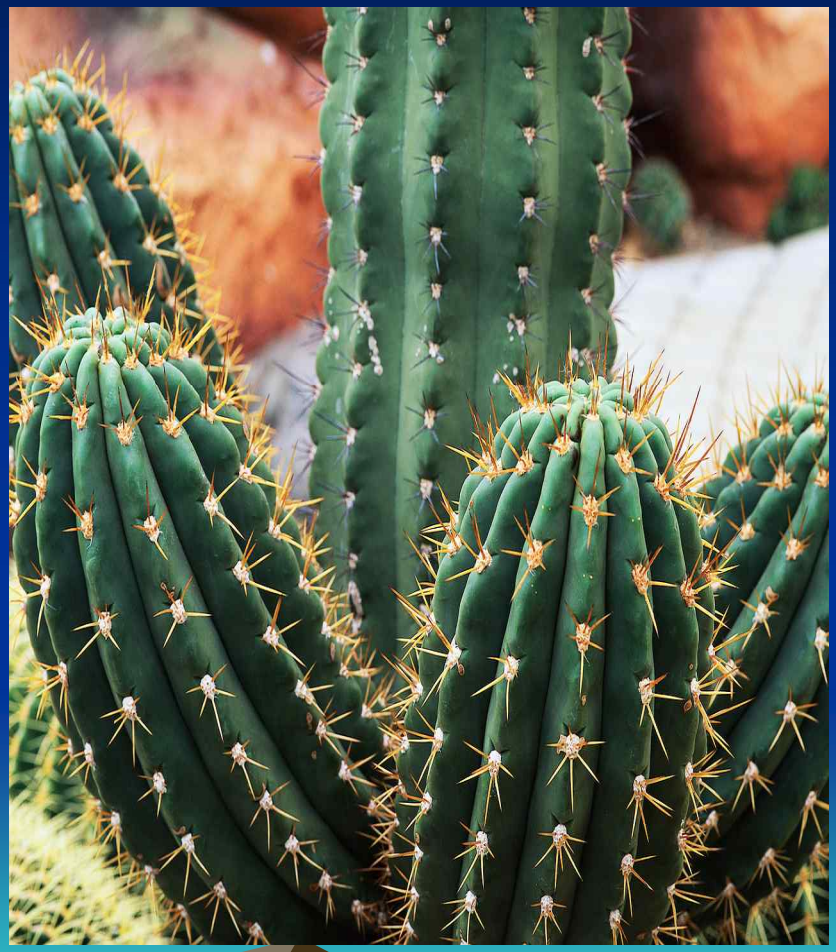
CRF Definitions

- **Descriptors:**
  - German
    - Ich bin mude…
  - Korean
    - In one study, more gastrointestinal Sx in Korean women with breast cancer vs USA sample;



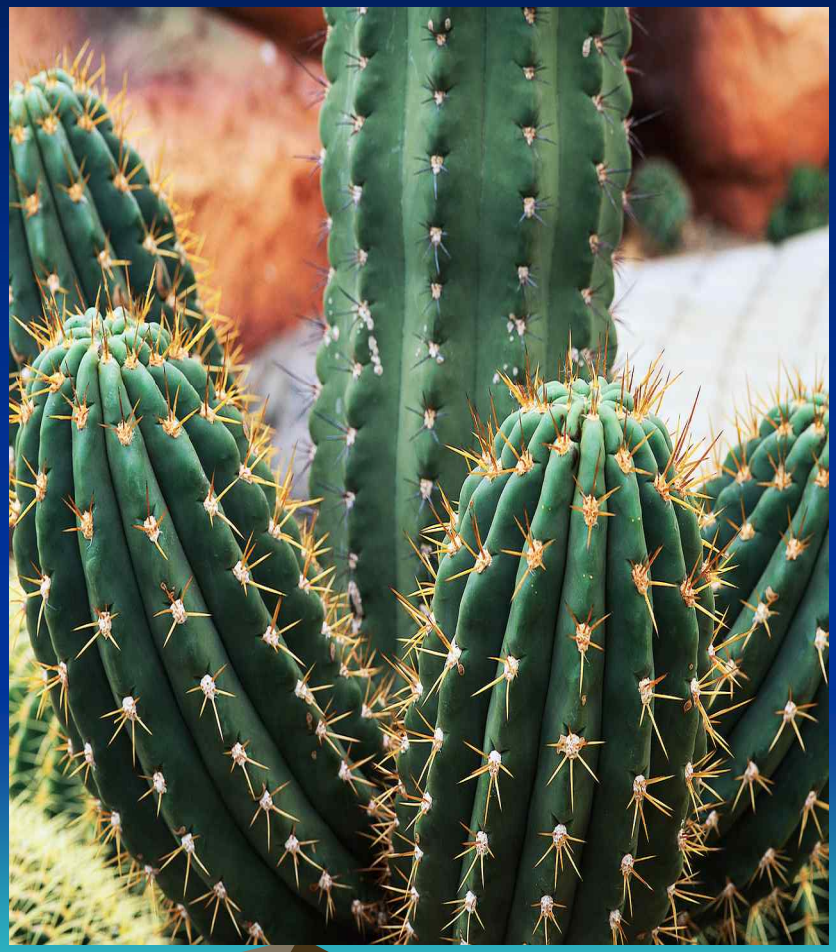
CRF Definitions

- **Descriptors:**
  - Energy, vitality, vigor descriptors respond differently as PRO measures in intervention studies
    - Than tiredness fatigue & exhaustion
  - These terms may be measuring different constructs
  - Assess & measure them separately in intervention studies & compare data.



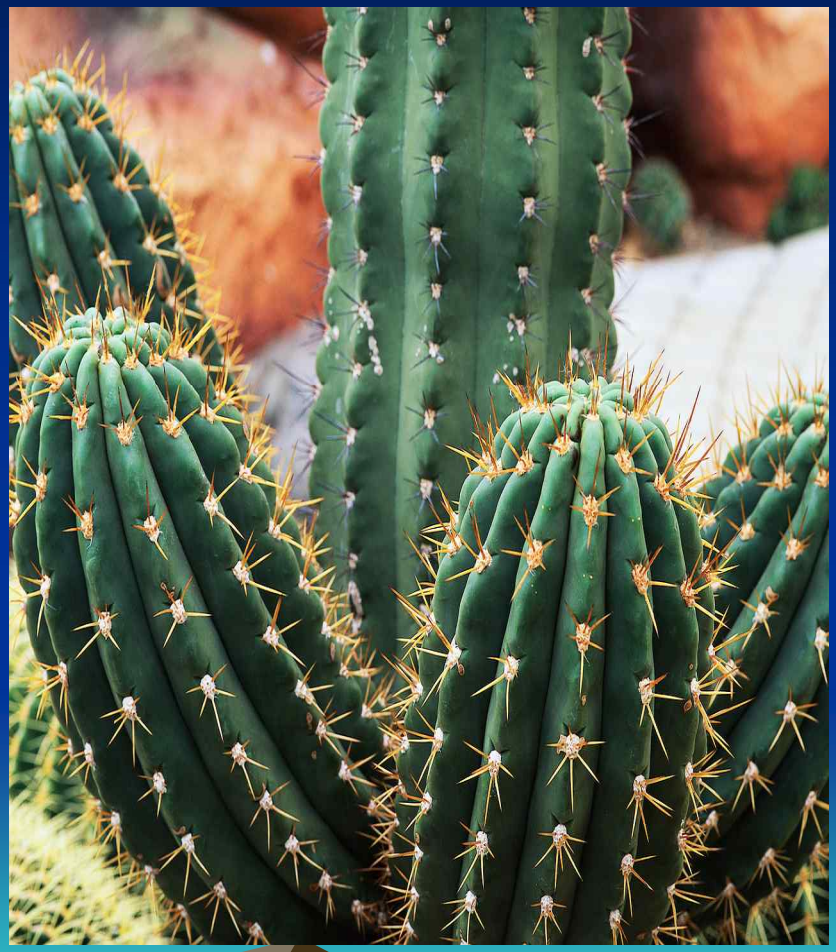
CRF Definitions

- **Case Definitions:**
  - Based on emerging evidence
  - Need to use “cut scores” (≥ 4 0n 0-10 numeric rating scales)(NRS)
  - None =0, mild =1-3; moderate =4-6. severe =7-10
  - Avoid analyzing & reporting only average/mean scores
  - Other attempts to define a case definition include comparing CRF rating with MOS-SF-36 vitality subscale scores



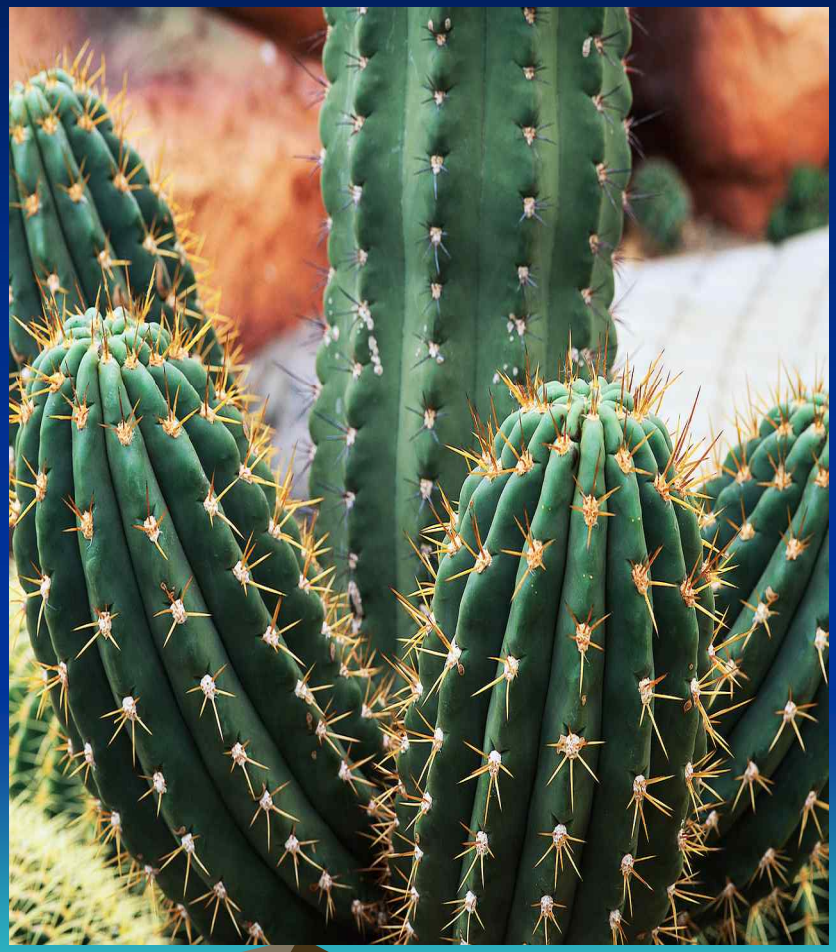
CRF Definitions

- **CRF ICD-10 Proposed Syndrome Criteria:**
  - 1st "heroic" attempt at case definition
  - Never were submitted for ICD-10 inclusion
  - Recent consensus conference: Not based on a wide range of evidence; set the bar "too high"



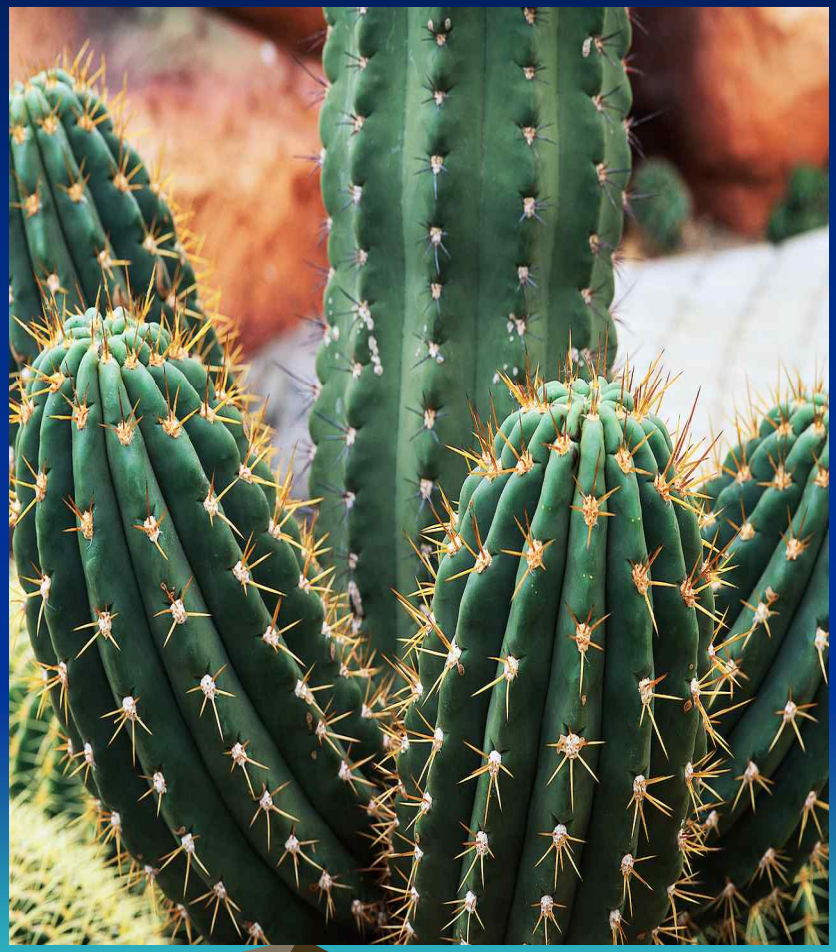
CRF Definitions

- **Phenotypes**
  - Different manifestations
  - Need more homogenous samples to tease this out
  - May vary by disease stage & type of treatment
  - Examples:
    - Weakness is not a common phenotype in women with it may be in advanced, palliative care patients with muscle wasting;
    - Sudden fatigue is another example that occurs



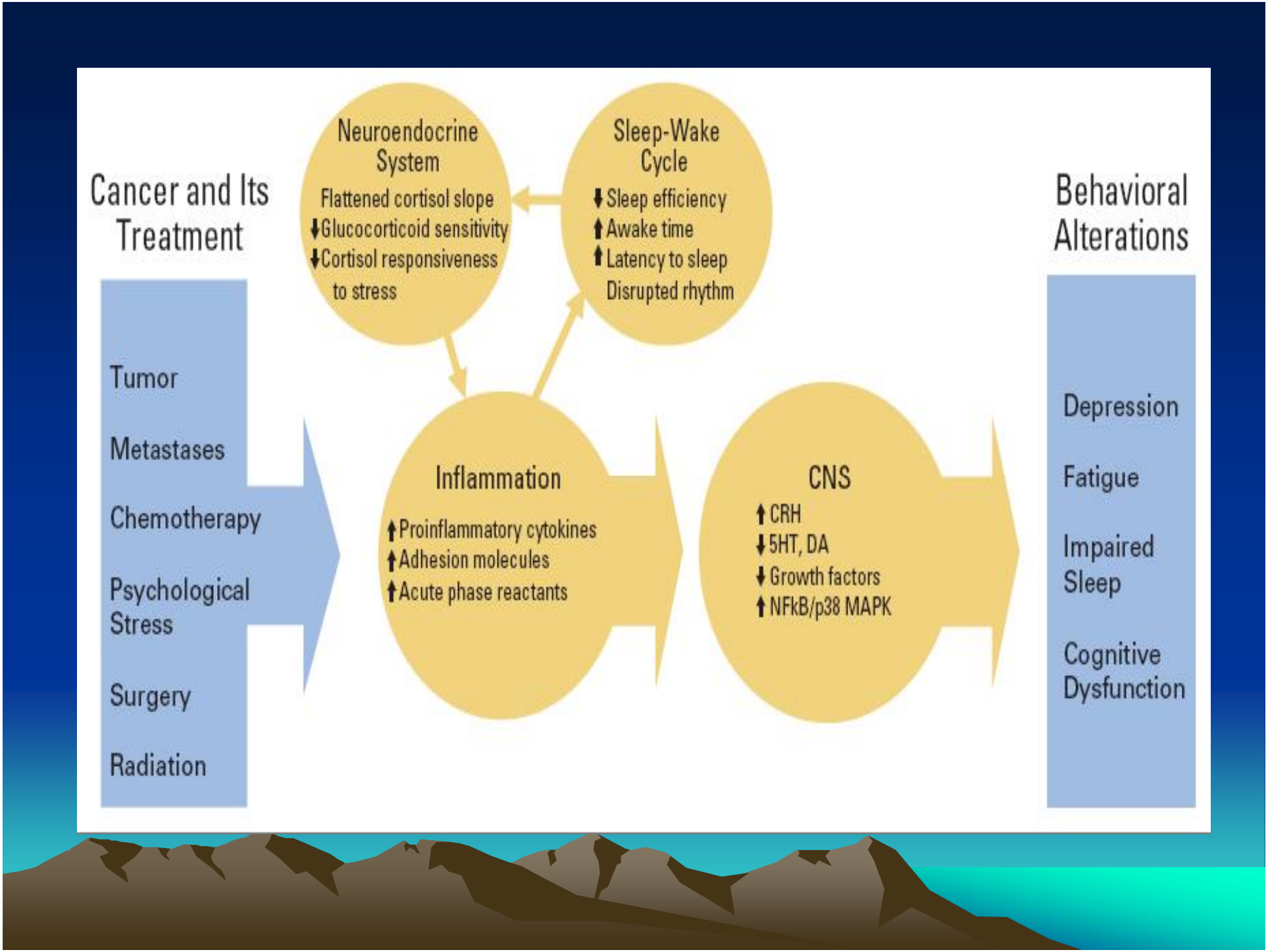
CRF Definitions

- Use newer statistical tests (Taxometric):
  - To analyze/reanalyze continuous data at the individual item level & to
  - Compare with better defined homogeneous samples & qualitative data



CRF Underlying Mechanisms

- Most research thus far
  - Descriptive & correlative
  - Not causal;
- Recent systematic reviews list several possible mechanisms
  - Gene polymorphisms
  - Altered circadian rhythmicity
  - Immune Dysregulation
  - Serotonin & neurotransmitter dysregulation
- Proinflammatory cytokines
- Hypothalamic-Pituitary-Adrenal Axis Dysregulation
- Vascular endothelial growth factors
- Disruption in adeosine triphosphate metabolism


Cancer and Its Treatment
Tumor
Metastases
Chemotherapy
Psychological Stress
Surgery
Radiation
Neuroendocrine System
Flattened cortisol slope
Glucocorticoid sensitivity
Cortisol responsiveness to stress
Sleep-Wake Cycle
Sleep efficiency
Awake time
Latency to sleep
Disrupted rhythm
Inflammation
Proinflammatory cytokines
Adhesion molecules
Acute phase reactants
CNS
CRH
5HT, DA
Growth factors
NFkB/p38 MAPK
Behavioral Alterations
Depression
Fatigue
Impaired Sleep
Cognitive Dysfunction

CRF Measurement

- Several systematic reviews describe
  - Multiple-item intensity scales
  - Multiple-item, multi-dimensional scales
  - Single item intensity scales
- What remains not well-studied:
  - Whether multidimensional scales
    - Give additional data to guide treatment planning
  - What constitutes a clinically significant difference with intervention studies
  - Timing, frequency, & correlations with subjective & objective measures

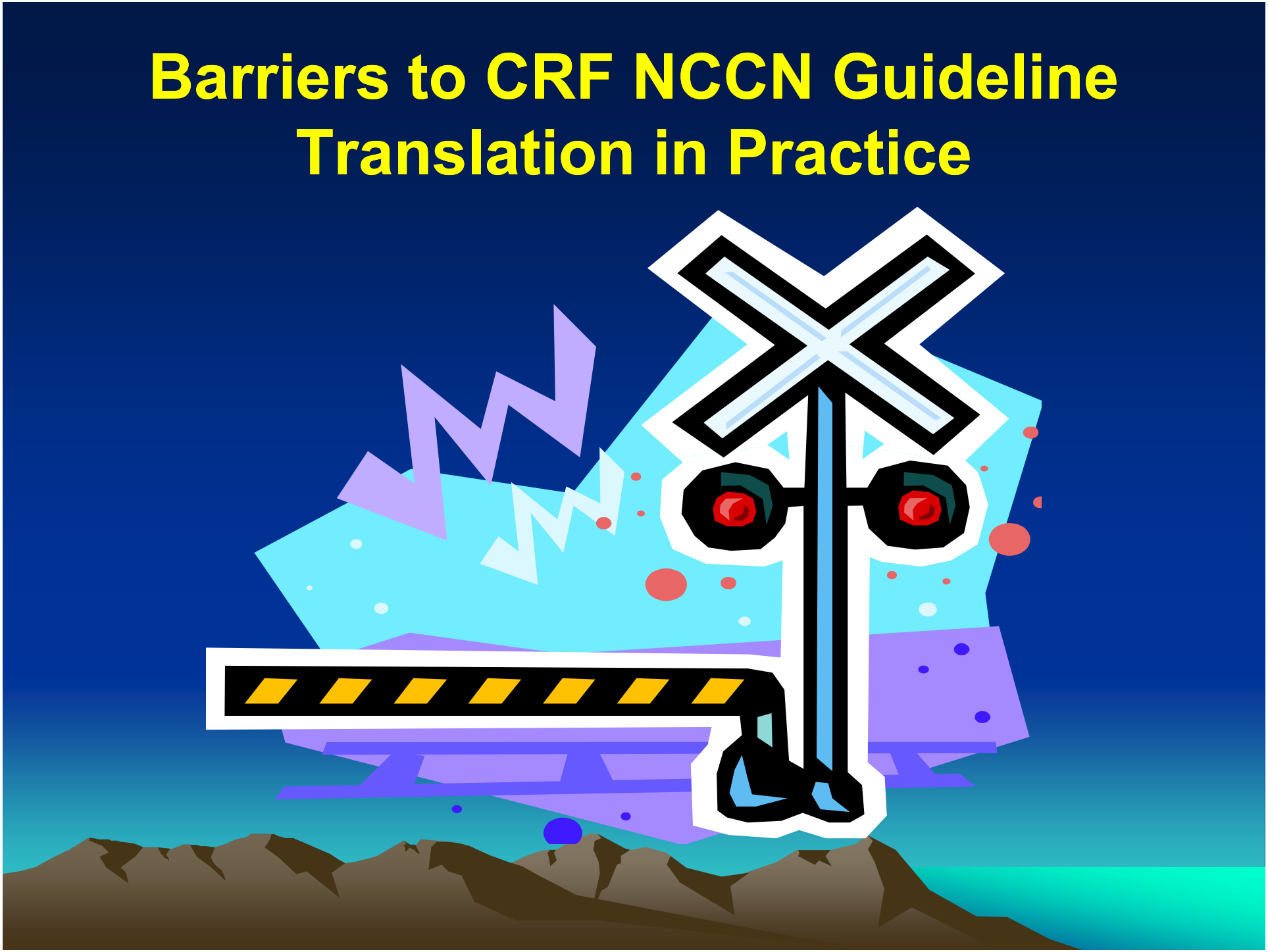
CRF Management

- Provider education is essential
  - **ONS CRF 6th vital sign symposium (2007)(N=1000)**
    - **50% of healthcare providers (mostly nurses)**
    - **Only somewhat familiar with the NCCN CRF Guidelines**
    - **41% were not even aware that the guidelines existed**
  - **NCCN web-based survey (N= >1000)(2009)**
    - **1/3 not aware of the guidelines**
    - **34% of oncologists (N=293/863) were unaware of them**
    - **An additional 32% of oncologists were aware of the guidelines**
      - **But had not accessed them during the past month**
  - Clearly studies are needed to evaluate guideline educational & dissemination programs with providers
  - And their effects on outcomes

CRF Management

- 5/6 educational studies demonstrated
  - Decreased CRF in the experimental groups receiving the intervention
  - Why did this happen so consistently
- Sample sizes ranged between 60-400 patients in the effective trials
  - Whereas the one "ineffective"trial may have been underpowered with a randomized sample of 40 patients
- Need to study biologically why this is happening
  - Perhaps the impact of stressors including CRF is being reduced & patients are feeling more empowered
  - We may even be seeing a subsequent impact on proinflammatory cytokine release from a nurse-led educational intervention…
- In 3/6 of these studies
  - The intervention effect was sustained at one month (N=2) and 3 months later (N=1)
- Similar components
  - Short sessions (10-60 minutes in length)
  - Information about CRf
  - Self-care or coping skills
  - Balancing activity with rest
  - Must be directed specifically toward CRF
- More study is needed
  - In homogeneous samples
  - On treatment, in survivors, & in palliative care/advanced cancer patients
  - In combination with other modalities to see if moderate effect sizes can be enhanced (i.e., exercise)

Barriers to CRF NCCN Guideline Translation in Practice



Barriers to CRF Guideline Translation in Practice (Borneman et al, 2007; Piper et al, 2008)

- **Provider-Related Barriers:**
  - May not recognize the prevalence or significance of CRF in patients/family members
  - May view other signs & symptoms as being more important than CRF
  - May not recognize that there are effective methods to assess & treat CRF
  - May not feel comfortable discussing CRF when there is little known about underlying mechanisms for CRF
  - May view the CRF guideline as too complex, too long & not feasible to implement

Barriers to Translating CRF Guidelines in Practice (Borneman et al., 2007; Piper et al., 2008)

- **Patient-Related Barriers:**
  - May not want to "bother" the provider; may view CRF as just "something I have to live with"
  - May think that if they report CRF, they may be viewed as a "complainer"
  - May fear that their treatment may be negatively affected
  - May not realize personally how much CRF has affected them
  - May not realize how important it is to report CRF to their provider
  - May fear that CRF means that their cancer is "getting worse"

Barriers to Translating CRF Guidelines in Practice (Borneman et al., 2007; Piper et al., 2008)

- **Setting-Related Barriers:**
  - Symptom assessment & management not prioritized in clinical settings
  - As a consequence, CRF & symptoms are not routinely or systematically assessed, managed or documented
  - Pain the only symptom assessed & managed & this required a mandate by the Joint Commission on Accreditation of Healthcare Organizations (JCO)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REDUCING
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PAIN & FATIGUE
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BARRIERS TO TRANSLATING NCCN PAIN & FATIGUE GUIDELINES INTO PRACTICE: A PROSPECTIVE STUDY (Ferrell, Piper, Borneman, Sun, Koczywas, & Uman, 2005-2010)(NCI)

- **Purpose**
  - Translate NCCN pain & fatigue guidelines into practice by reducing barriers (patient, provider & system)
  - Develop a model for others to translate guidelines into practice
- **Framework**
  - Barriers & antecedents (demographic, number of symptoms, gender, disease stage)
- **Design**
  - Longitudinal, 3-phased study

BARRIERS TO TRANSLATING NCCN PAIN & FATIGUE GUIDELINES INTO PRACTICE: A PROSPECTIVE STUDY (Ferrell, Piper, Borneman, Sun, Koczywas, & Uman, 2005-2010)(NCI)

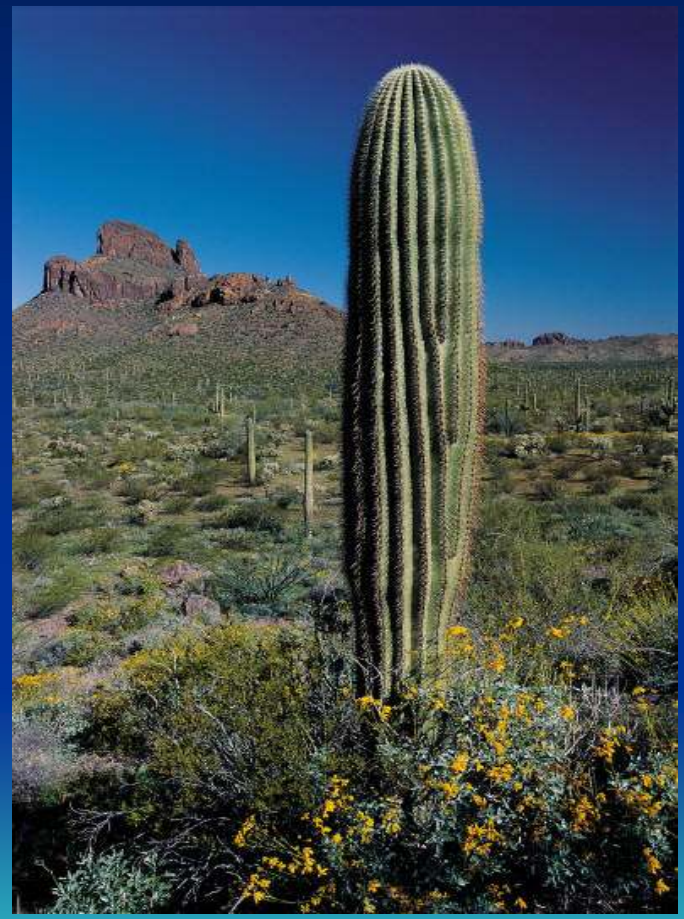
- **Phase 1: (N=83)**
- **Usual care baseline, 1 & 3 mos**
- **Phase 2: (N=104)**
  - **High intensity**
  - **Research staff involved with systematic Pt & MD education, 2 wk follow ups by phone or clinic;**
  - **Chart audits & feedback**
- **Phase 3:**
  - **Lower research intensity: APRNs & MDs do teaching, replicable model; see sustainability.**

BARRIERS TO TRANSLATING NCCN PAIN & FATIGUE GUIDELINES INTO PRACTICE: A PROSPECTIVE STUDY (Ferrell, Piper, Borneman, Sun, Koczywas, & Uman, 2005-2010)(NCI)

- **Phase 1: (N=83)**
  - Many of the barriers in literature were documented
  - Lack of supportive care referrals & documentation
- **Phase 2: (N=104)**
  - Those diagnosed 4 yrs or more had the most negative beliefs about CRF being able to be managed
  - Exercise will make CRF worse; better to rest & sleep more
    - Need to include exercise barriers teaching
  - Sensory CRF scores decreased over time in advanced patients
  - Future intervention trials, need to assess disease response to treatment; may confound the intervention
- **Phase 3:**
  - In progress. Accrual stops November, 2009.

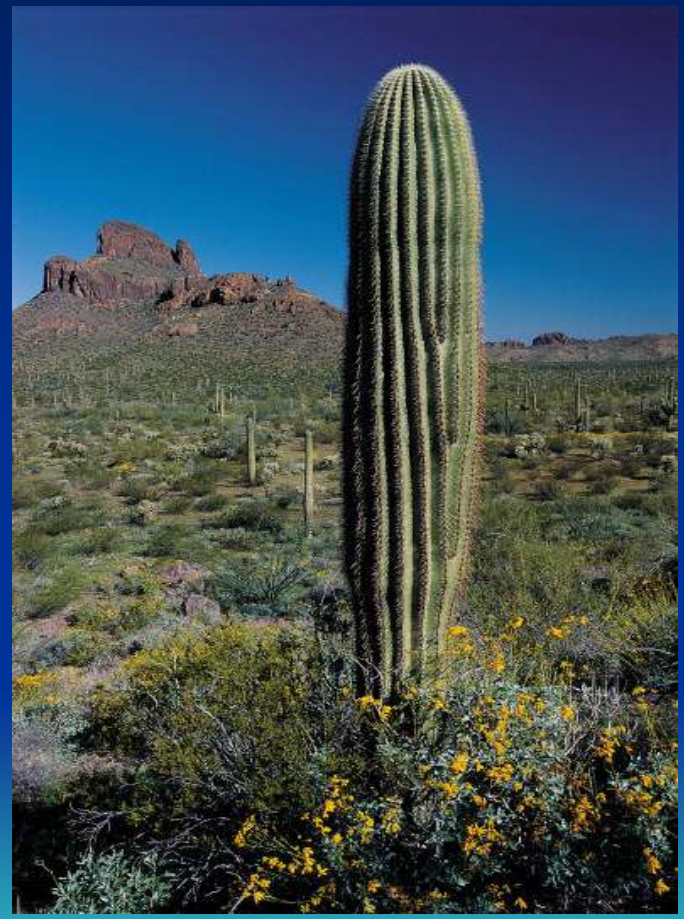
CRF Management

- Assessment & Screening
- Differential diagnosis
- General principles
  - Current disease & treatment status & tailor treatments accordingly
- Goals of Treatment
  - Target primary underlying cause; “Gang of 7”: & consider using multimodal Rx



CRF Management

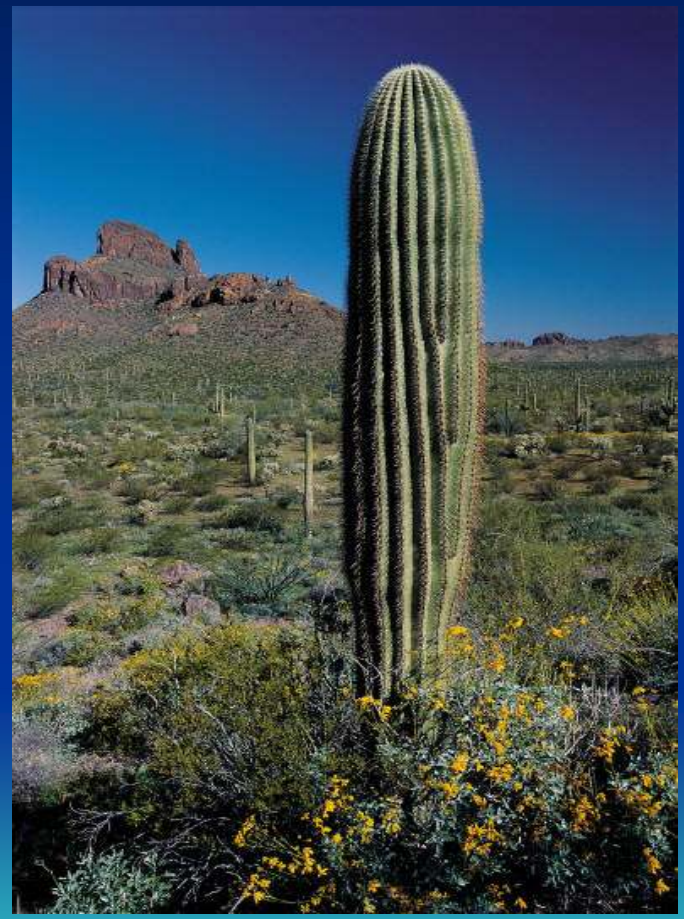
- Anemia
  - While ESA's were associated with slight reductions in CRF, many of the studies used an energy
  - Limited CRF studies with blood transfusions or iron supplements
  - Refer to NCCN anemia guidelines



CRF Management

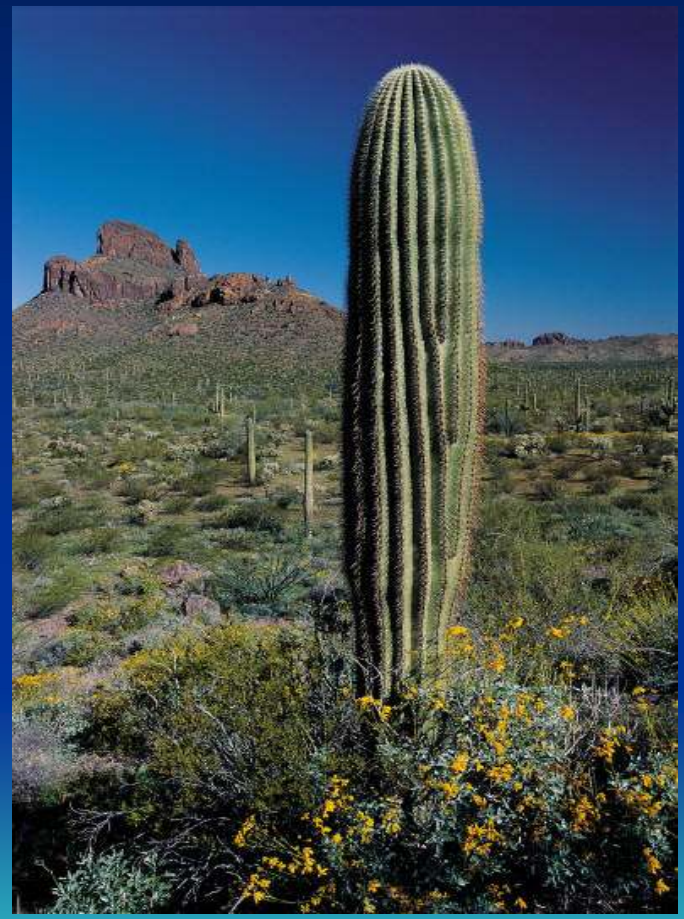
Comorbidity

- Changes in comorbidity status & medications may affect CRF; Need to assess & reassess over time in patients & consider referrals to other internists & specialists as needed;
- Pharmacologic consultation may be helpful.



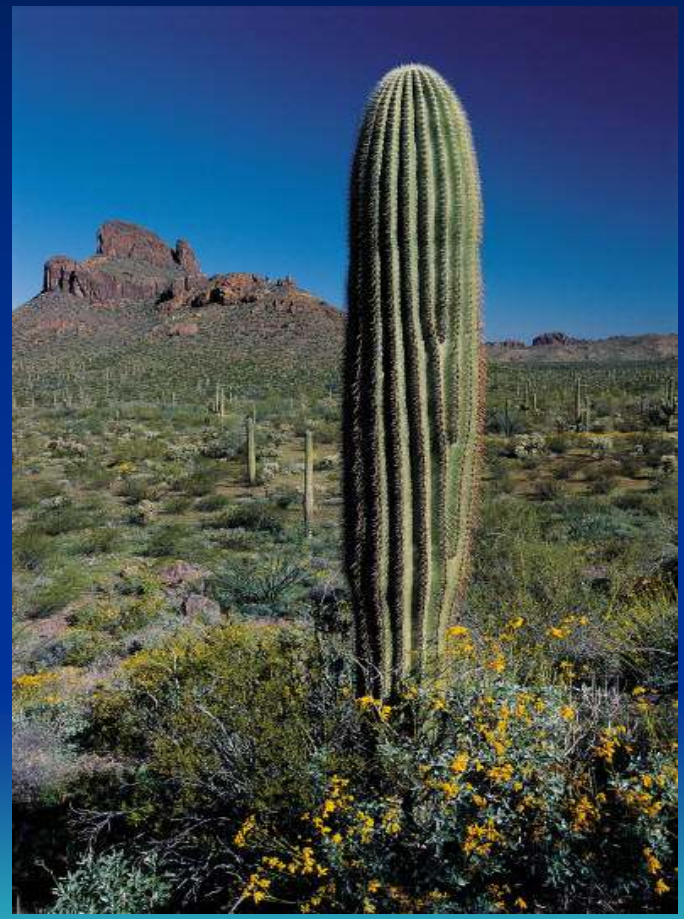
CRF Management

- **Activity level**
  - Include patient & provider education about exercise barriers
    - Consider "teachable" moments for behavioral lifestyle changes
  - Assess & screen periodically for development of deconditioning
  - Prescribe an exercise program (only 20% of MDs do this & they don't appreciate just how important that for patients to hear it from their providers)



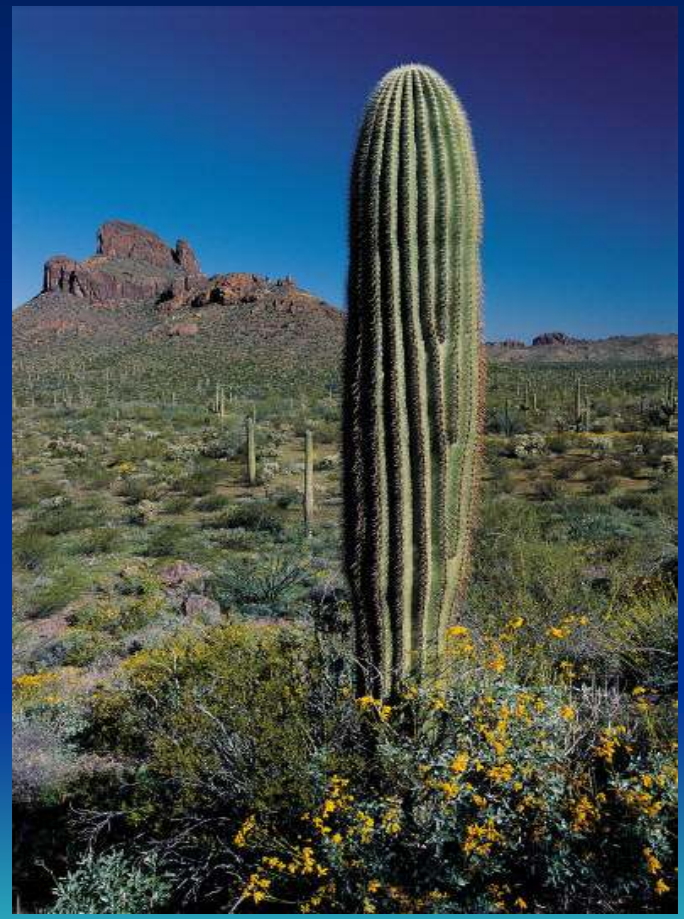
CRF Management

- **Activity level**
  - Consider referrals to Physical Medicine, Physical Therapy & Occupational Therapy
  - Category 1 evidence exists for a variety of exercise programs & positive effects on CRF, disease prevention, side effect management & recurrence; See several recent systematic reviews



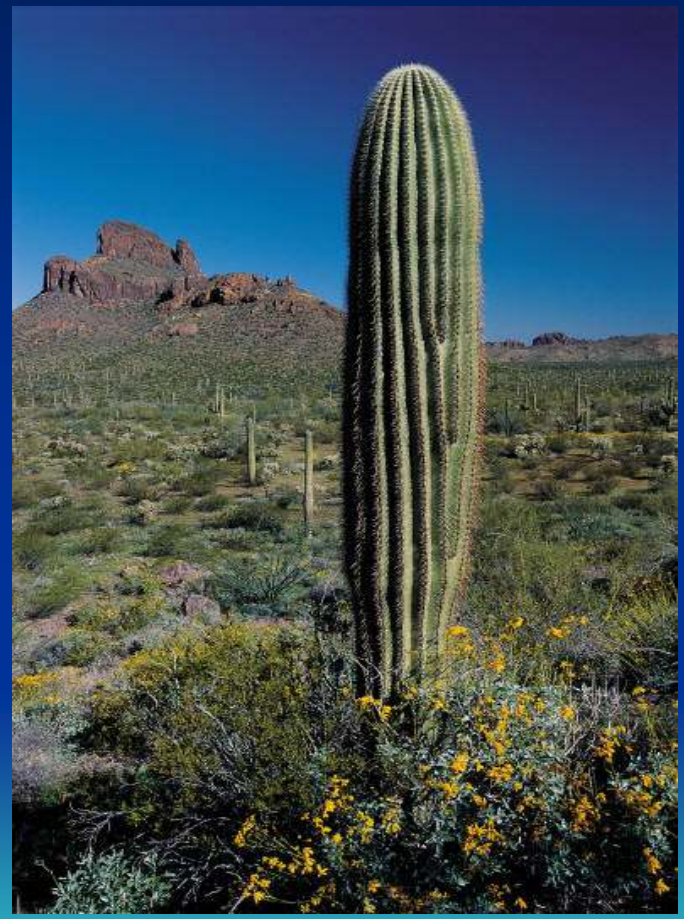
CRF Management

- **Emotional Distress**
  - Refer to the NCCN Emotional Distress Guidelines
  - Several cognitive-behavioral interventions & CAM therapies are effective in reducing CRF
  - Refer to the NCI PDQ website for pharmacologic interventions;
  - Paroxitine (Paxil) treated depression but not CRF in one large RCT



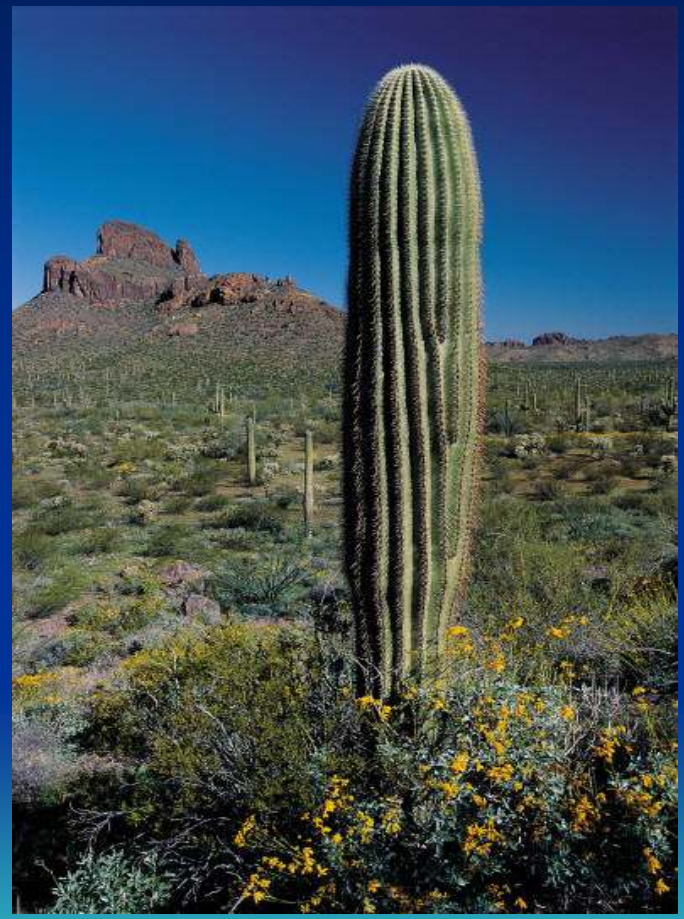
CRF Management

- **Nutrition**
  - Not well-studied
  - Two studies showed no effect on CRF, but may have been under-powered
  - More study is needed
  - Systematic review being initiated by MASCC CRF & Nutrition Study Groups



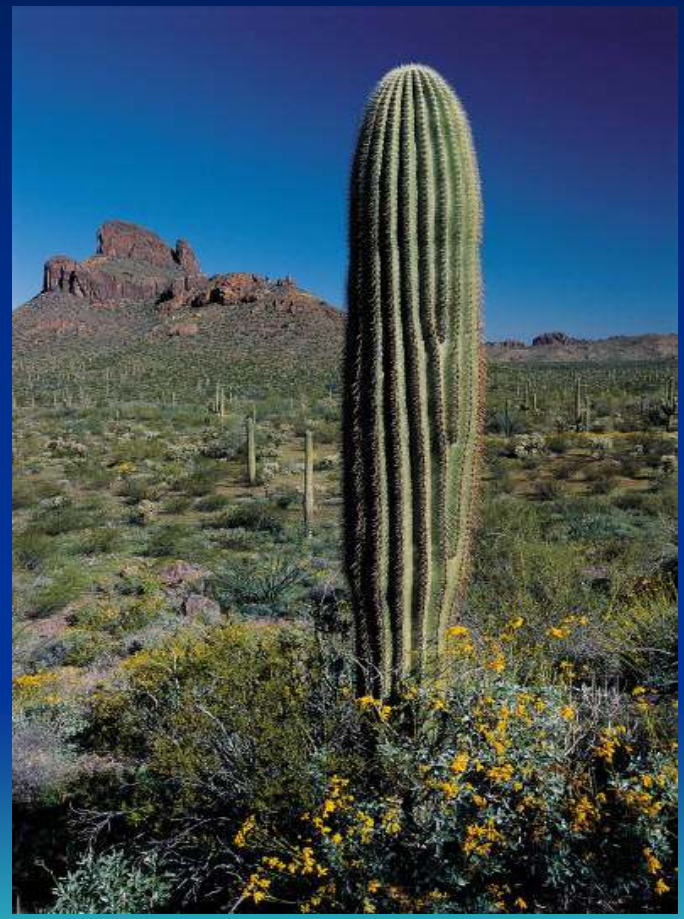
CRF Management

- **Pain**
  - Teach patients about barriers to pain management
  - Refer to NCCN pain guidelines
  - Refer to NCI PDQ guidelines for pharmacologic therapies



CRF Management

- **Sleep**
  - One large RCT demonstrated reduction in sleep disturbance but did not have any effect on CRF
  - More study is clear warranted
  - In the interim include cognitive behavioral strategies (i.e., teaching about stimulus control, sleep restriction, relaxation training & sleep hygiene)
  - Consider referral to sleep specialist;
  - See NCI PDQ website for pharmacologic interventions & NCCN CRF Guidelines for psychostimulant implications



CRF Summary & Future Directions

- Use homogenous samples in studies
- Avoid equating energy items with fatigue items
- Explore the use of proven educational, cognitive-behavioral, and exercise strategies for managing CRF
- Evaluate use of multimodal strategies in treating CRF
- Combine PROs with biological marker measures
- Analyze data for unique phenotypes
- Work with other international colleagues to advance the CRF research agenda & submission of a case definition to the WHO ICD-11 version.

Questions & Discussion