Neuropsychiatric Aspects of Cancer

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Overview

- Epidemiology
- Inflammatory response and BBB
- Depression
- Anxiety

Depression & Anxiety In Cancer Patients

- The prevalence of anxiety and depression in those with cancer has been reported to be around 25-30%
- Symptoms can alter patients' quality of life and overall functional status
- Almost universally remain undiagnosed and undertreated in the cancer population and in almost all other medical populations
'Normal' Reactions to Cancer

- Usual emotional response to cancer includes:
  - Initial shock and disbelief
  - Irritability
  - Altered appetite and sleep patterns
  - Difficulty in concentration and focus
  - Social withdrawal and ability to engage in 'usual' daily activities
  - Fears about future

- Symptoms usually resolve after 3-8 weeks
  - Family support
  - Social support
  - Structure of cancer treatment

Recovery From Medical Illness & Physical Injury

<table>
<thead>
<tr>
<th>Adaptive Stages</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>Survival Fear</td>
<td>Cheeration</td>
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<tr>
<td>Problem of Pain</td>
<td>Medication</td>
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<tr>
<td>Search for Meaning</td>
<td>Validation</td>
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<tr>
<td>Investment in Recuperation</td>
<td>Education</td>
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<tr>
<td>Acceptance of Losses</td>
<td>Legitimization</td>
</tr>
<tr>
<td>Investment in Rehabilitation</td>
<td>Commendation</td>
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<tr>
<td>Reintegration of Identity</td>
<td>Termination</td>
</tr>
</tbody>
</table>

Stress Response to Medical Illness & Trauma

- Sympathetic nervous system activation
- Endocrine 'stress response'
  - Prolactin hormone secretion
  - Insulin resistance
- Immunological changes
  - Cytokine production
  - Acute phase reaction
  - Neutrophil leukocytosis
  - Lymphocyte proliferation
Stress Response and BBB

NEUROTRANSMITTER DYSFUNCTION
BASAL GANGLIA-THALAMO-CORTICAL CIRCUIT DYSFUNCTION

DELIRIUM

Metals
Heavy metals (lead, manganese, mercury); carbon monoxide, toxins

Infection
Encephalitis; meningitis, general paresis, HIV/AIDS, sepsis, pneumonia, endocarditis

Inflammation/Degeneration
Autoimmune disease, paraneoplastic limbic encephalitis, lysosomal storage diseases

Trauma/Surgery
Subdural and epidural hematomas, lacerations, contusion

Postoperative Trauma
↓ Cardiac output (co)
Cardiac failure, cardiac arrest, cardiac arrhythmia

↓ Oxygen Saturation
Hypoxia and anoxia secondary to pulmonary, anesthesia, anemia

Vascular
Hypertensive encephalopathy; cerebral arteriosclerosis; intracranial hemorrhage or thromboses; circulatory collapse (shock): autoimmune vasculopathies

Metabolic Derangements
Endocrinopathies
Diabetic coma and shock; uremia; myxedema; hyperthyroidism, parathyroid dysfunction; hypoglycemia; hepatic failure; porphyria; severe electrolyte or acid base disturbances; remote side effects of carcinoma, Cushing Syndrome

CNS States
Epilepsy; postictal states; aneurysm

Vitamin Deficiencies
Deficiencies of thiamine (Wernicke-Korsakoff syndrome), niacin (pellagra), B12 (pernicious anemia)

Etiopathophysiology of Delirium
↓ ACh
↑ DA
↓ GABA
↑ GLU

IRS and Brain Perfusion

Frontal-Subcortical Dysfunction

Frontal Lobe Circuits

Risk Factors for ‘Circuit’ Disruption

- Substrate
- Acute/Critical Illness
- iatrogenic
- Age (older)
- Acalculia
- immobilization (e.g., catheters, restraints)
- Neuronal degeneration
- Anemia
- Medicated (e.g., sedatives, benzodiazepines)
- Traumatic brain injury
- Infarction/sepsis/SIRS
- Sleep disturbances
- Atrophy
- Hypodensity
- Psychiatric illness
- Metabolic disturbances (for example, sodium, calcium, BUN, lactate, ammonia)
- Hypertension
- Respiratory disease
- Vision/hearing impairment
- High severity of illness


Depression & Cancer

- One of the most common psychiatric disorders in the world
- One of the leading causes of disability worldwide
- Fewer than 25% have access to effective treatments despite ability to diagnose reliably
- Prevalence in cancer:
  - 38% for major depression
  - 58% for depression spectrum

Prevalence of Depression in Cancer

<table>
<thead>
<tr>
<th>Authors</th>
<th>Cancer Site</th>
<th>Sample Site</th>
<th>Diagnostic Method</th>
<th>Affective Disorders</th>
<th>Adjustment Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depp-Strickland et al., 1999</td>
<td>Mood Disorders</td>
<td>DSM-IV</td>
<td>5%</td>
<td>15%</td>
<td></td>
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<tr>
<td>Case et al., 1998</td>
<td>Mood Disorders</td>
<td>DSM-IV</td>
<td>15%</td>
<td>45%</td>
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<tr>
<td>Priebe et al., 2003</td>
<td>Mood Disorders</td>
<td>DSM-IV</td>
<td>15%</td>
<td>20%</td>
<td></td>
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<tr>
<td>Repper et al., 2009</td>
<td>Mood Disorders</td>
<td>DSM-IV</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Prevalence of Cancer by Site

<table>
<thead>
<tr>
<th>Prevalence by Cancer Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>23% - 50%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>22% - 57%</td>
</tr>
<tr>
<td>Breast</td>
<td>13% - 46%</td>
</tr>
<tr>
<td>Lung</td>
<td>11% - 44%</td>
</tr>
<tr>
<td>Colon</td>
<td>13% - 25%</td>
</tr>
<tr>
<td>Gynecological</td>
<td>12% - 23%</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>8% - 19%</td>
</tr>
<tr>
<td>Gastric</td>
<td>11%</td>
</tr>
</tbody>
</table>

Massie JM, J Natl Cancer Inst Monogr, 2004
### Depression & Risk Factors
- Younger age
- Personality factors (anger, pessimism)
- History of trauma and losses
- Previous psychiatric history
- History of SUDs
- Social isolation and lack of support
- Socioeconomic status
- Advanced disease
- Physical function and status
- Tumor location
- Poorly controlled symptomatic management

### Diagnosis of Depression in Medical Illness
- Depression symptoms are a spectrum ranging from sadness to major depressive episodes
- Mood changes can be a challenge to assess in those who feel life threatened by illness and disease states
- Diagnosis of depression in ‘physically healthy’ individuals relies heavily on the presence of somatic symptoms (e.g., fatigue, anorexia, weight loss, insomnia, etc.)

### Major Depressive Diagnostic Criteria
1. At least 5 of the 9 below symptoms for 2 weeks or more, most of the time, almost every day, and this is a change from prior level of functioning. One of the symptoms must be either (a) depressed mood, or (b) loss of interest:
   - **A. Depressed mood**
   - **B. Loss of interest or pleasure in most all activities**
   - **C. Weight loss or gain**
   - **D. Insomnia (or hypersomnia)**
   - **E. Feeling fatigued or with decreased energy**
   - **F. Agitated or slowed behavior**
   - **G. Thoughts of worthlessness or guilt**
   - **H. Reduced ability to think, concentrate, or make decisions**
   - **I. Thoughts of suicide or death**

2. Symptoms cause great distress or difficulty in functioning at home, work, or other
3. Symptoms not caused by substances or a medical condition
4. Symptoms not due to normal grief
Depression & Cancer

Four approaches have been described in assessment of depression on medical illness

- Inclusive approach
  - Counts all symptoms of depression whether or not they may be secondary to physical illness.

- Etiologic approach
  - Counts depressive symptoms only if it is presumed not secondary to physical illness.

- Exclusive approach
  - Eliminates symptoms such as anorexia, fatigue, etc which can be secondary to cancer, and employs other depression criteria. Increases specificity, lowers sensitivity which may result in lower prevalence and under-diagnosis.

- Substitutive approach
  - Replaces indeterminate symptoms such as fatigue (frequently secondary to physical illness) with cognitive symptoms such as indecisiveness, brooding, and hopelessness.

Depression Screening and Measurements

- Distress Thermometer
- PHQ-9
- Beck Depression Inventory
- Brief Symptom Inventory 18 – Depression Subscale
- The Hospital Anxiety and Depression Scale

Management of Depression

- When to consider pharmacotherapy:
  - Prior positive responses to antidepressants
  - Moderate to severe symptom burden
- PHQ-9 scores 10-14: consider antidepressants
- PHQ-9 scores >15: antidepressants strongly encouraged
- Past history of severe depression (hospitalizations, suicidality, protracted disability)
- Significant disturbance of sleep or appetite, or agitation
- Co-morbid condition that may benefit from antidepressants (e.g., chronic pain)
- Relevance of maintenance pharmacotherapy: prior history of recurrence and/or severity
- Patient preference
- Shared decision-making
Management of Depression

Serotonin Reuptake Inhibitors (SSRIs):
- Fluoxetine, paroxetine, sertraline, citalopram, escitalopram

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):
- Venlafaxine, duloxetine, desvenlafaxine, levomilnacipran

Norepinephrine-Dopamine Reuptake Inhibitor (NDRI):
- Bupropion

Miscellaneous Agents
- Mirtazapine
- Vilazodone
- Vortioxetine

Tricyclics (TCAs)
- E.g., nortriptyline, amitriptyline, imipramine, clomipramine

Management of Depression

Selecting an antidepressant
- Generic SSRIs, SNRIs, bupropion or mirtazapine are reasonable first line agents.
- No evidence for superiority of one agent or class for “usual” outpatient depression.

Clinical considerations
- Prior good response/tolerability ➔ re-try same agent
- Depression with anxiety and/or irritability ➔ SSRIs
- Severe depression and/or chronic pain ➔ SNRIs
- Predominant weight loss, insomnia ➔ mirtazapine
- Motivated for smoking cessation ➔ bupropion
- Prior intermittent missed doses ➔ fluoxetine
- On tamoxifen ➔ venlafaxine, citalopram, escitalopram

Management of Depression

The following agents are relatively less favorable first line agents when concerns exist about:
- Tamoxifen: X ➔ fluoxetine, paroxetine, bupropion, duloxetine
- Cytochrome P450 2D6 inhibition of metabolism of co-prescribed substrates (e.g., codeine, tamoxifen, TCAs, propranolol): X ➔ fluoxetine, paroxetine, duloxetine, bupropion
- Weight gain: X ➔ mirtazapine, paroxetine
- Drowsiness: X ➔ mirtazapine, paroxetine, trazodone
- Hypertension: X ➔ trazodone
- Hypertension: X ➔ SNRIs
- Seizure risk: X ➔ bupropion
- QTc prolongation: X ➔ citalopram, escitalopram
- Abrupt discontinuation-emergent reactions: X ➔ paroxetine, SNRIs
Anxiety & Fear: Definitions

- **Definition of anxiety?**
  - A diffuse, unpleasant, vague sense of apprehension often a response to an imprecise or unknown threat.

- **Definition of fear?**
  - An emotional response to a known or definite threat.
  - Principle emotion with delirium/encephalopathy/seizure activity

Anxiety & Fear: Epidemiology

- 19% have anxiety disorder
- Subclinical anxiety increases this to 22.6%
- 13% with depression and 16.5% with subclinical symptoms
- Prevalence in oncology is 15%-40%

Anxiety in Cancer: Risk Factors

<table>
<thead>
<tr>
<th>Pre-Cancer Risk Factors</th>
<th>Post-Treatment Risk Factors</th>
</tr>
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<tbody>
<tr>
<td>Female gender</td>
<td>Treatment non-response or metastasis</td>
</tr>
<tr>
<td>Younger age</td>
<td>Respiration compromise or O2E</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Pain or Somatic sensations/sympthms</td>
</tr>
<tr>
<td>History of alcohol use disorder</td>
<td>High dose steroid administration</td>
</tr>
<tr>
<td>History of psychiatric illness</td>
<td>Seizures and/or CNS changes</td>
</tr>
<tr>
<td>Personality traits (e.g., pessimism)</td>
<td>Neuropathy and/or-endocrine dysfunction</td>
</tr>
</tbody>
</table>
Anxiety & Fear: Hypoxia

Anxiety & Fear: IRS

Anxiety & Fear: Pathophysiology
Acute Stress and Neuroendocrine Measures

Anxiety & Fear: Neuropeptide-Y

- 36-amino acid neuropeptide that acts as a neurotransmitter in the brain and in the autonomic nervous system of humans
- Functions:
  - Reduces anxiety and stress and associated with resiliency
  - Decreases pain perception
  - Affects circadian rhythm
  - Lowers BP
  - Decreases seizurogenic activity
  - Increases food intake and fat storage

Anxiety & Fear: Stress and Neuropeptide-Y
Anxiety & Fear: NF-κB

- NF-κB regulation is essential to many aspects of our health including:
  - Cellular development
  - Cellular survival
  - Immune system
  - Diseases associated with dysregulation of NF-κB
    - Atherosclerosis
    - Arthritis
    - Cancer
    - Diabetes
    - Infectious bowel disease
    - Stroke
    - Neuropsychiatric illness (?)

Anxiety Disorders – DSM-5

- Separation anxiety disorder
- Selective mutism
- Specific phobia
- Social phobia/panic disorder
- Panic disorder
- Panic attack
- Agoraphobia
- Generalized anxiety disorder
- Anxiety due to general medical disorder
- Substance-induced anxiety disorder
- Anxiety, unspecified


Anxiety & Fear: Morphine
Anxiety & Fear: Anxiety Disorders

- Anxiety due to a general medical condition
- General anxiety
- Panic attacks
- Adjustment reaction
- Acute stress reaction
- Specific phobia

- Excessive anxiety and worry more days than not
  - The person finds it difficult to control the worry
  - Anxiety and worry associated with 3 or more of the following:
    - Restlessness or feeling keyed up
    - Being easily fatigued
    - Difficulty concentrating or mind going blank
    - Irritability
    - Muscle tension
    - Sleep disturbance
Anxiety & Fear: Anxiety Disorders

- Anxiety due to a general medical condition
- Generalized anxiety
- Panic attacks
  - Discrete period of intense fear or discomfort, in which 4 or more of the following develop abruptly and reach a peak within 10 minutes:
    - Palpitations
    - Sweating
    - Trembling or shaking
    - Sensations of shortness of breath or smothering
    - Feeling of choking
    - Chest pain
    - Nausea or abdominal distress
    - Dizziness
    - Derealization or depersonalization
    - Fear of losing control or going ‘crazy’
    - Fear of dying
    - Paresthesias
    - Chills or hot flashes
- Adjustment reaction
  - Due to an identifiable stressor occurring within 3 months of onset of stressor
  - Marked distress in excess of what would be expected
  - Impairment in social or occupational functioning
  - Once stressor has stopped, the symptoms do not persist for more than another 6 months
  - May manifest as anxiety, mixed-type, with disturbance of conduct, mixed disturbance of emotions and conduct, or unspecified

Acute stress reaction
- Exposure to traumatic event
- Dissociative symptoms
- Avoidance of stimuli that elicit memories of event
- Anxiety and hyperarousal
- Lasts a minimum of 2 days and a maximum of 4 weeks
Anxiety & Fear: Anxiety Disorders

- Anxiety due to a general medical condition
- General anxiety
- Panic attacks
- Adjustment reaction
- Acute stress reaction
- Specific phobia
  - Marked or persistent fear (>6 months) that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation

Fear of Cancer Recurrence

- The fear or worry that cancer will return or progress in the same organ or in another part of the body
- Reported by 22-74% of people with a history of cancer
  - Women > men
  - Younger patients
  - Less formal education
- May last a LONG time
- First year after diagnosis
  - Overall distress goes down
  - Fear of recurrence remains

Anxiety & Fear: Principles for Integrated Settings

- Screening
  - GAD-7
  - Beck Anxiety Inventory (BAI; 21 items)
  - ICU
    - VAS
    - Faces Anxiety Scale

- Interventions
  - Pharmacotherapy (mild to severe)
  - ACT/CBT oriented interventions (mild to moderate)
  - Pharmacotherapy + CBT oriented interventions (moderate to severe)

- Maintain medications + CBT boosters for 1-2 years
Anxiety & Fear: Pharmacotherapy
- Benzodiazepines
  - Clonazepam
  - Lorazepam
  - Diazepam
  - Valproate
  - Carbamazepine
  - Bupropion
  - TCAs
    - Nortriptyline
  - Dopamine antagonists
    - Quetiapine
    - Olanzapine
  - AEDs
    - Gabapentin
    - Pregabalin
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
    - Venlafaxine
  - SSRI/SNRIs
    - Citalopram/escitalopram
    - Sertraline
  - Dopamine antagonists
    - Pramipexole
    - Dopamine
  - Opioids

Adapting EBT to Integrated Cancer Care Settings
- EBT for Anxiety
  - Anxiety disorders share common etiology, symptoms, maintaining processes, etc.
  - Cognitive: future-oriented, perceived threat
  - Behavioral: avoidance
  - Physiological: autonomic arousal
  - Similar treatment approach across different anxiety presentations
- Cancer Care Setting
  - Population-based care
  - Brief episodes of care
  - Goals of improving function and reducing symptoms
  - Patient education, activation, engagement in own health care
  - Education and targeted self-management skills for at home practice
- Goals: Increase awareness and teach coping skills

Anxiety & Fear: 6 Brief Interventions
- Adapted from existing evidence-based interventions
  - Psycho-education
  - Relaxation training
  - Mindfulness & acceptance based behavioral interventions
  - Cognitive restructuring
  - Exposure
  - Behavioral activation
- Focus on: Adults and GAD, panic, phobias, adjustment (Not PTSD, social anxiety, or OCD)
Psycho-Education Resources

- VA CIH handouts: Anxiety, Panic attacks, Action Plan for Anxiety, Stress Fact Sheet, Stress Response and How It Affects You, etc.
  - Patient education site: [www.mirecc.va.gov/visor1/clinical_resources.asp](http://www.mirecc.va.gov/visor1/clinical_resources.asp)
  - Other handouts
    - Panic about info: [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
    - Intro to anxiety disorder: [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
    - Fight or flight response: [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
    - Safety behavior: [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
    - Breathing: [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
  - ADAA website
    - Overview: [www.adaa.org/understanding-anxiety](http://www.adaa.org/understanding-anxiety)

Relaxation Training Resources

- Encourage regular at-home practice and PRN use
  - Websites with a good selection of audio files (with spoken instructions and calming music) to guide patients through various relaxation exercises
    - [www.health.ucsd.edu/specialties/mindfulness/programs/mbsr/Pages/audio.aspx](http://www.health.ucsd.edu/specialties/mindfulness/programs/mbsr/Pages/audio.aspx)
    - [http://marc.ucla.edu/body.cfm?id=22](http://marc.ucla.edu/body.cfm?id=22)
    - [http://www.mirecc.va.gov/visor1/docs/therapists_guide_to_brief_cbtmanual.pdf](http://www.mirecc.va.gov/visor1/docs/therapists_guide_to_brief_cbtmanual.pdf)
  - For patients: handouts with instructions
    - VA CIH Patient Education Materials (Relaxation fact sheet, General relaxation exercise, deep breathing, abdominal breathing, etc.)
    - Other handouts with instructions
      - [http://www.therapistaid.com/content/0081.pdf](http://www.therapistaid.com/content/0081.pdf)
      - [http://www.therapistaid.com/content/0097.pdf](http://www.therapistaid.com/content/0097.pdf)
      - [http://psychology.tools/progressive-muscle-relaxation.html](http://psychology.tools/progressive-muscle-relaxation.html)
      - [http://psychology.tools/relaxed-breathing.htm](http://psychology.tools/relaxed-breathing.htm)
      - [http://www.therapistaid.com/content/0132.pdf](http://www.therapistaid.com/content/0132.pdf)
  - Websites with a good selection of audio files (with spoken instructions and calming music) to guide patients through various relaxation exercises
    - [http://www.mckinley.illinois.edu/units/health_ed/relax_relaxation_exercises.htm](http://www.mckinley.illinois.edu/units/health_ed/relax_relaxation_exercises.htm)
    - [http://www.uhs.wisc.edu/health-topics/stress/relaxation.shtml](http://www.uhs.wisc.edu/health-topics/stress/relaxation.shtml)

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  - [http://www.therapistaid.com/content/0148.pdf](http://www.therapistaid.com/content/0148.pdf)
  - [http://www.mckinley.illinois.edu/units/health_ed/relax_relaxation_exercises.htm](http://www.mckinley.illinois.edu/units/health_ed/relax_relaxation_exercises.htm)
  - [http://www.uhs.wisc.edu/health-topics/stress/relaxation.shtml](http://www.uhs.wisc.edu/health-topics/stress/relaxation.shtml)
  - [http://marc.ucla.edu/body.cfm?id=22](http://marc.ucla.edu/body.cfm?id=22)
Mindfulness and Acceptance Based Behavioral Therapies

- Eliciting the patient’s values
  - Verbal inquiry, e.g., What matters most to you in your life?
  - List or worksheet
    - http://www.therapistaid.com/content/0147.pdf
    - http://psychology.tools/values.html
- Identify what valued activities are being avoided due to anxiety
  - Help them set 1-3 specific goals that would move them in the direction of their priority values
  - Troubleshoot by identifying potential barriers and developing corresponding coping strategies

Cognitive Restructuring Resources

- For patients: Handouts and worksheets
  - VA On-Patient Education Materials (Cognitive distortions, Fixing cognitive distortions):
  - Countering anxious thoughts:
    - http://www.therapistaid.com/content/0003.pdf
  - Cognitive distortions:
    - http://www.therapistaid.com/content/0047.pdf
  - Decatastrophizing:
    - http://psychology.tools/decatastrophizing.html
  - CBT thought record:
    - http://psychology.tools/cbt-thought-record.html
  - Worry thought record:
    - http://psychology.tools/worry-thought-record.html
  - Unhelpful thinking styles:
    - http://psychology.tools/unhelpful-thinking-styles.html
  - Challenging negative thoughts:
    - http://www.therapistaid.com/content/0109.pdf

Exposure Therapy Resources

- Exposure practice form:
- Exposure hierarchy:
  - http://www.therapistaid.com/content/0053.pdf
- Interoceptive exposure examples:
  - http://psychology.tools/interoceptive-exposure.html
- Avoidance hierarchy:
  - http://psychology.tools/avoidance-hierarchy.html
Behavioral Activation Resources


- For patients: Handouts and worksheets
  - Behavioral activation: [http://www.therapistaid.com/content/0022.pdf](http://www.therapistaid.com/content/0022.pdf)
  - Values assessment: [http://psychologytools.com/values.html](http://psychologytools.com/values.html)
  - Values self-exploration: [http://www.therapistaid.com/content/0147.pdf](http://www.therapistaid.com/content/0147.pdf)
  - Values clarification: [http://www.therapistaid.com/content/0023.pdf](http://www.therapistaid.com/content/0023.pdf)
  - Weekly schedule: [http://www.therapistaid.com/content/0108.pdf](http://www.therapistaid.com/content/0108.pdf)
  - Activity list: [http://www.therapistaid.com/content/0106.pdf](http://www.therapistaid.com/content/0106.pdf)