GBMC HEAD AND NECK GRAND ROUNDS

PREVENTION AND TREATMENT PARADIGMS: WHERE DOES ONE STOP AND THE OTHER BEGIN?
PREVENTION OF DEPRESSION IN HEAD AND NECK CANCER

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Disclosures: Grant and Research Support

- Federal: National Institute of Mental Health R01 MH079420
- Industry:
  - Matching drug and placebo for current R01: Forest Laboratories Inc.
- Panel member NCCN Head and Neck
Understand the role of depression in Head and Neck Cancer Patients

Recognize the blurring of prevention and treatment strategies in HNC

Apply a prevention of depression strategy for your HNC patients
What Does a Surgeon Know About Depression?
“The melancholic juice is in excess not only in melancholia but also in cancer.”

Galen 2nd Century A. D.
Psycho-social factors seemed to be the deciding factor.
Important Psycho-social Factors

- Social Support
- Satisfaction with consultation and information
- Behavioral factors (alcohol and tobacco)
- Depressive symptoms
- Personality

Llewellyn et al, Oral Oncol 2005 41:440-54
Incidence of Depression in Cancer

- 20% of all cancer patients
- 40% of head and neck patients (second highest of all cancers)
- Depressive symptoms even higher
- Tends to peak at 2-3 months following initiation of treatment
Environmental Factors Modulating the Effect of Loss

- Concurrent life events
- Resultant change in lifestyle
- Lack of interpersonal support
- Deficient social skills
- Symbolic meaning of loss

Kaplan and Sadock’s Textbook of Psychiatry 7th Edition Chapter 14
Depression in HNC

- Up to half of HNC patients become depressed
- Peaks rates are in the midst of treatment
- High rates of depression related to:
  - Disease often affects speech, eating, and facial appearance
  - High rates of co-morbid alcohol and tobacco use
  - Prolonged and aggressive treatments
Depression in HNC

- Depression is rarely recognized or treated.
- When depression occurs:
  - Lengthens hospital stays.
  - Reduces:
    - adherence with medical treatment.
    - quality of life.
    - survival – one mechanism through treatment delay.
Suicide in Head and Neck Cancer

- Recent suicide estimates\(^2\):
  - general population - 15.8 per 100,000 person-years
  - cancer patients - 33.6 per 100,000 person-years
  - HNC patients - 50.5 per 100,000 person-years

- Thus, patients with HNC have over 3 times the risk of the general population and 1.5 times the average cancer patient's risk\(^2\)

- Cancer of the larynx and tongue make up 2% of all cancers but account for 19% of all suicides related to cancer\(^1\)

Vegetative symptoms are the same for depression and treatment
Focus on physical rather than psychiatric findings
Expertise
Therapeutic nihilism regarding psychiatric conditions

Wooley et al, and Thompson et al, 6th International
and now it's time for something completely different
Aimed at persons at high risk of developing a disorder

maximum achievable health gain*/minimum effort needed to produce that health gain**

- *Attributable fraction = the number of percentage points the incidence rate of depression would be reduced if the adverse effects of the risk indicator were completely blocked
- **Expressed as NNT or the number of patients who would need to receive a preventive intervention to avoid 1 new case of depression
What is Treatment and What is Prevention in HNO?

- Elective neck dissection or radiation
- Postoperative radiation therapy
- Chemoradiation (CRT) for adverse histology
- PEG tube placement prior to concomitant primary CRT
- Antibiotics prior to surgery
How Information is Presented to the Patient Matters
- An emotional assessment:
- if one has a favorable or unfavorable impression of the benefit of a given therapy, one will unconsciously assign fewer risks, and vice versa
- You are the agent of information delivery
- You have a duty to be clear and unbiased in your delivery
- You have an obligation to assist the patient in making the correct choice for them
Role of Adjuvant Chemotherapy and Radiation

- Bernier et al: European Organization for Research and Treatment of Cancer (EORTC trial 22931)*
  - 334 subjects 1994-2000
- Cooper et al: Radiation Therapy Oncology Group (RTOG trial 9501)*
  - 416 subjects 1995-2000
- Bernier, Cooper, et al: comparative analysis#
  - Radiation 2 Gy fractions
  - Cisplatin 100mg/meter² days 1, 22, and 43

# Head Neck 27;2005;843-50
Radiation versus chemoradiation

Local regional control: 72% versus 82%*

3 yr Progression free survival: 37% vs 47%*

3 yr Overall survival: 45% versus 55%

Severe side effects (>Grade 3) 34% vs 77%*

Death due to Treatment: 0/231 vs 4/228

* Significant differences
EORTC Results

- Radiation versus chemoradiation
  - Local regional control: 69% versus 82%*
  - Progression free survival: 36% vs 47%*
  - Overall survival: 40% versus 53%*
  - Severe side effects (≥ Grade 3) 21% vs 44.5%*
- Death from treatment: 1/167 in both

* Significant differences
How information is presented matters

- 30% improved survival
- 1 additional person out of 10 will be alive at 3 years if chemotherapy is added
- 9 of 10 people will receive chemotherapy without benefit and likely with more complications
- 98% of people survive the treatment
- 2 out of 100 people will be killed by this treatment
Number needed to treat for one person benefited or harmed

- Number needed to help for disease specific survival
  - 10 people

- Number needed to harm for acute grade 3 or 4 toxicity
  - 2.3 people
First level 1 evidence for chemoradiation as an adjunct
- Indications are positive margins and extra-capsular extension of nodal tumor

NCCN recommendations were changed to include adjuvant chemoradiation
So What Can We Do?
Portraits of Care
Mark Gilbert
Important Psycho-social Factors

- Social Support
- Satisfaction with consultation and information
- Behavioral factors (alcohol and tobacco)
- Personality
- Depressive symptoms

Llewellyn et al, Oral Oncol 2005 41:440-54
What about the Psycho-social Factors Can We Improve?

- Social support is hard to improve
- Information
  - Wrote a book called “Cancers of the Mouth and Throat: A Patient’s guide to treatment”
- Tobacco and alcohol
  - Cessation programs available in our hospital
  - Ask at each visit
What about the Psycho-social Factors Can We Improve?

- Tobacco and alcohol
  - Programs for cessation
  - Use of anti-depressants
- Personality change?
  - Peter Kramer “Listening To Prozac”
  - Suggested that some patients became better than well
  - Could a Prevention Trial work?
Learned Helplessness (LH) and Prevention

- LH results from exposing animals to severe, inescapable stress
- Considered to be an animal model for clinical depression.
- In the rat, LH can be prevented by treatment with antidepressant drugs, if these agents are administered in repeated doses prior to inescapable stress exposure
- This maintains levels of cortical serotonin and prevents stress-induced depletion of serotonin in proportion to prevention of stress-induced depressive behavior

Prophylactic treatment of HNC patients with an antidepressant will:
- prevent or minimize depressive symptoms in patients undergoing treatment for HNC
- improve quality of life
- impact longevity by improving adherence

Methods

- IRB approval obtained at UNMC and Methodist Hospital
- Prospective, randomized, double blind, placebo-controlled trial
- Citalopram given to patients with newly diagnosed or recurrent head and neck cancer about to undergo treatment who were NOT depressed
- Citalopram dose: 20 mg x 1 week, then 40 mg daily
28 were randomized and began medication
- 2 in citalopram group dropped out due to side effects (GI), one in the placebo group withdrew consent
- 25 completed visit one
  - 2 in placebo withdrew, both due to hospitalization, 1 each for depression and failure to thrive
- 23 completed the study (13 in citalopram group)
Results of the Hamilton Depression Rating Scale (HDRS) at weeks 4, 8, 12, 16, or at any visit indicating a trend toward significant differences between the placebo and citalopram hydrobromide groups (an HDRS score of >=15)


Copyright restrictions may apply.
Quality of Life (UW-QOL): Median Change from Baseline

* Wilcoxon p-value = 0.14, UW-QOL = University of Washington Disease Specific Quality of Life Questionnaire
Survival vs. Death or Recurrent Disease after 24 Months:

By Mood Status During the Acute Study

By Mood Status During the Acute Study

<table>
<thead>
<tr>
<th>Recurrence or Death</th>
<th>Disease Free</th>
</tr>
</thead>
</table>

Never Depressed Group

Depressed Group

$X^2 = 4.9$, $p=0.03$

Lazure KE, Head & Neck, 31 (7), 888–892, 2009
Depression which emerges during the treatment of HNC may be preventable

Preventing depression may impact the quality and quantity of life of persons with cancers of the head and neck

Mechanism of prevention is undetermined as is potential impact on mortality

Prevention: an underused paradigm?
The PROTECT Study Team

- William J. Burke
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- Deborah S. Heimes
- Delores A. McArthur-Miller
- Rosella Squires
Prevention Of depression in patients being TreEated for head and neck Cancer Trial (PROTECT)

PI: Burke, WJ, Co-PI: Lydiatt, WM

Patients Present for Treatment of Cancer of the Head and Neck

Consenting Patients Evaluated for Current Major Depression

Patients Without Major Depression Begin Protocol

Treatment of HNC Begins

• 2-14 Weeks Duration
• Surgery, Radiation, Chemotherapy Either Singly or Combined

Treatment of HNC Ends

Post-Treatment Follow-up

Prophylactic Study Begins

• 16 Weeks Double-blind
• 10-20 mg Escitalopram or Matching Placebo

One Week Taper

11 Week Follow-up

Key Measures:
1) Rate of new episodes of major depression
2) Quality of Life
3) Alcohol & Tobacco Use

Key Measure:
Delay or Interruptions in Cancer Treatment
298 Patients Screened

160 Agreed to Participate

12 Patients Ineligible to Participate
QIDS-SR or QIDS-C16 score ≥ 11 9
Not able/willing to return for follow-up 1
Received anti-depressants in the past week 1
Not diagnosed with epidermoid cancer and meets MINI criteria for depression 1

148 Patients Randomized

74 Given Escitalopram
14 Not Evaluable (Only BL Visit)
Withdraw consent 5
Unacceptable side effects from meds 6
Need to take Lorazepam 1
Never started – fear of side effects 1
Surgical complications – missed visits 1

74 Given Placebo
9 Not Evaluable (Only BL Visit)
Withdraw consent 6
Unacceptable side effects from meds 2
Didn’t want to take medication 1

60 Evaluable
Completed 16 weeks with no depression 30
Became depressed 6
Withdrew consent 12
Unacceptable side effects from meds 8
Resides in nursing home – can’t take meds 2
Primary MD recommended stopping study 1
Patient died 1

65 Evaluable
Completed 16 weeks with no depression 28
Became depressed 16
Withdrew consent 15
Unacceptable side effects from meds 3
Resides in nursing home – can’t take meds 1
Using Lorazepam QD for RT 1
Wants to stay on antidepressant 1

138 Declined to Participate
 Doesn’t want to take study drug 20
Lack of time 15
Lack of interest 5
 Doesn’t want to chance receiving placebo 3
Too ill 2
Distance 2
Other reason 11
Not Reported 80
### Baseline Characteristics of Randomized Study Participants by Group

<table>
<thead>
<tr>
<th></th>
<th>Escitalopram (n=74)</th>
<th>Placebo (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.2 (11.3)</td>
<td>62.8 (12.5)</td>
</tr>
<tr>
<td>Male</td>
<td>59 (79.7)</td>
<td>59 (79.7)</td>
</tr>
<tr>
<td>Race - White</td>
<td>72 (97.3)</td>
<td>71 (96.0)</td>
</tr>
<tr>
<td>Smoker at Baseline</td>
<td>16 (21.9)</td>
<td>18 (24.7)</td>
</tr>
<tr>
<td>Study Site: UNMC</td>
<td>33 (44.6)</td>
<td>35 (47.3)</td>
</tr>
<tr>
<td>MCC</td>
<td>41 (55.4)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>Clinical Stage: II</td>
<td>17 (23.0)</td>
<td>18 (24.3)</td>
</tr>
<tr>
<td>III/IV</td>
<td>57 (77.0)</td>
<td>56 (75.7)</td>
</tr>
<tr>
<td>Initial Treatment: Surgery (Not Biopsy)</td>
<td>42 (56.8)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>Radiation with/without Chemotherapy</td>
<td>32 (43.2)</td>
<td>35 (47.3)</td>
</tr>
</tbody>
</table>
Cox proportional hazard regression model comparing the two treatment groups after controlling for age, sex, baseline smoking status, study site, stage of disease, and initial treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>Chi-Square</th>
<th>P-value</th>
<th>Hazard Ratio</th>
<th>HR 95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram vs. Placebo</td>
<td>-0.997</td>
<td>0.487</td>
<td>4.19</td>
<td>0.04</td>
<td>0.37</td>
<td>0.14, 0.96</td>
</tr>
<tr>
<td>Site (MCC vs. UNMC)</td>
<td>0.367</td>
<td>0.465</td>
<td>0.62</td>
<td>0.43</td>
<td>1.44</td>
<td>0.58, 3.59</td>
</tr>
<tr>
<td>Sex (Female vs. Male)</td>
<td>0.110</td>
<td>0.575</td>
<td>0.04</td>
<td>0.85</td>
<td>1.11</td>
<td>0.36, 3.45</td>
</tr>
<tr>
<td>Stage (II vs. III/IV)</td>
<td>-0.602</td>
<td>0.647</td>
<td>0.86</td>
<td>0.35</td>
<td>0.55</td>
<td>0.15, 1.95</td>
</tr>
<tr>
<td>Initial Treatment</td>
<td>1.282</td>
<td>0.489</td>
<td>6.88</td>
<td><strong>0.009</strong></td>
<td>3.61</td>
<td>1.38, 9.40</td>
</tr>
<tr>
<td>Age</td>
<td>0.008</td>
<td>0.020</td>
<td>0.14</td>
<td>0.70</td>
<td>1.01</td>
<td>0.97, 1.05</td>
</tr>
<tr>
<td>Baseline Smoking (No vs. Yes)</td>
<td>1.271</td>
<td>0.755</td>
<td>2.84</td>
<td>0.09</td>
<td>3.57</td>
<td>0.81, 15.66</td>
</tr>
</tbody>
</table>
Depression Free Survival for Placebo vs. Escitalopram

Survival from Onset of Depression

Test: $p = 0.042$

<table>
<thead>
<tr>
<th>Weeks</th>
<th>CENSOR</th>
<th>FAIL</th>
<th>TOTAL</th>
<th>MEDIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>49</td>
<td>16</td>
<td>65</td>
<td>.</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>54</td>
<td>6</td>
<td>60</td>
<td>.</td>
</tr>
</tbody>
</table>
Percent Reaching Primary Endpoint (QIDS-SR ≥ 11)

P = NS
Radiation Therapy

- Potentially curative
- Can be function preserving
- Continued advancements made (IMRT)
- Requires 6 or 7 weeks of daily therapy
- Requires specialized equipment
- Travel time can be significant
- Can be disfiguring and result in lack of function
# Escitalopram vs. Placebo: UW–Quality of Life Scale

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Health-Related QOL Last 7 Days M–H Chi-Square p-value</th>
<th>Overall QOL Last 7 Days M–H Chi-Square p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.84</td>
<td>0.20</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>0.31</td>
<td>0.14</td>
</tr>
<tr>
<td>8 Weeks</td>
<td>0.45</td>
<td>1.00</td>
</tr>
<tr>
<td>12 Weeks</td>
<td>0.82</td>
<td>0.64</td>
</tr>
<tr>
<td>16 Weeks</td>
<td>0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>20 Weeks</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>24 Weeks</td>
<td>0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>28 Weeks</td>
<td>0.02</td>
<td>0.05</td>
</tr>
</tbody>
</table>
### Frequency of Side Effects: FIBSER

<table>
<thead>
<tr>
<th></th>
<th>Placebo N (%)</th>
<th>Escitalopram N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of Side Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No side effects - present 25% of time</td>
<td>60 (96.7%)</td>
<td>52 (91.2%)</td>
</tr>
<tr>
<td>Present more than 25% of time</td>
<td>2 (3.3%)</td>
<td>5 (8.8%)</td>
</tr>
<tr>
<td>Fisher’s exact test, p=0.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intensity of Side Effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No side effects - mild</td>
<td>59 (95.2%)</td>
<td>49 (86%)</td>
</tr>
<tr>
<td>Moderate or greater</td>
<td>3 (4.8%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Fisher’s exact test, p=0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Burden of side effects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No side effects - mild</td>
<td>60 (96.8%)</td>
<td>54 (94.7%)</td>
</tr>
<tr>
<td>Moderate or greater</td>
<td>2 (3.2%)</td>
<td>3 (5.3%)</td>
</tr>
<tr>
<td>Fisher’s exact test, p=0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Depression linked to decreased plasticity in the hippocampus

- Chronic unpredictable stress:
  - decreases hippocampal expression of gene that regulates neuronal plasticity (neurintin)

- Antidepressants reverse this effect

- Increased expression of neurintin:
  - Prevents hippocampal atrophy
  - Prevents depressive behaviors associated with unpredictable stress

Conclusions

- Prophylactic escitalopram reduced the rate of emergent depression in HNC patients undergoing treatment for HNC (NNT=6.8)
- The rate of developing depression was significantly higher in patients receiving radiation as their primary therapy compared to surgery
- Those who received escitalopram reported statistically significant improvement in overall QOL for all three months following the randomized portion of the trial
Depression is a common and devastating comorbidity among head and neck patients
Prophylaxis is an under utilized paradigm
Ultimately, it is the strength, determination and courage of those who undertake treatment that win the day. Of them, we are in awe.
Thank You For Your Attention
Questions about Preventing Depression

- To prevent depression do we need to know the cause?
  - nature/genetic? nature/environment?
- If we could prevent depression could we prevent all causes or only some?
- What kinds of interventions might be beneficial and have acceptable risks?
- If we could prevent, should we?
# Prevalence of Depression and Comorbid Medical Illness

<table>
<thead>
<tr>
<th>Medical Illness</th>
<th>Rate of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery Disease</td>
<td>20 - 23%</td>
</tr>
<tr>
<td>Cancer</td>
<td>20 - 40%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 - 30%</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 - 34%</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>20 - 30%</td>
</tr>
<tr>
<td>Post-hip fracture</td>
<td>9 - 47%</td>
</tr>
</tbody>
</table>

Holmes JD, *Age Ageing* 2000; 29:537-546
Occurrence Rates of Newly Developed PSD Cases After the Prophylactic Use of Antidepressants

CI, confidence interval; PSD, poststroke depression; random, random-effects model; RD, rate difference; pooled RD, average effects based on individual RD.

# Conceptualizing Prevention

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td>Universal intervention</td>
<td>General public</td>
<td>Decrease incidence</td>
</tr>
<tr>
<td></td>
<td>Selected intervention</td>
<td>At risk subgroups</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indicated intervention</td>
<td>Symptomatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>individuals</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>Treatment</td>
<td>Identified cases</td>
<td>Decrease prevalence</td>
</tr>
<tr>
<td>Tertiary prevention</td>
<td>Maintenance</td>
<td>Identified cases</td>
<td>Prevent relapse/ recurrence</td>
</tr>
</tbody>
</table>

- Aimed at persons at high risk of developing a disorder

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<tr>
<td></td>
<td></td>
<td>individuals</td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology of Depression

- 10-25% of women will have depression in their lifetime
- 5-12% of men
- Sub-syndromal depression may occur twice as commonly as major depression
- Suicide (31,655 deaths in 2002 in US)
Pathophysiologica\nal Approach to Understanding Depression

- Heredity
  - Genes 11p, X, and 18p and q, plus others
  - Developmental environment-parent effect
- Life events (major loss)
- Biological stressors (thyroid, interferon, chemotherapy)

Why Depression in HNC?

- Prolonged and aggressive treatments
- Disease affects basic aspects of life including speech, eating, and facial appearance
- Treatment also affects key areas
- High rates of alcohol and tobacco use (80 and 90% respectively)
- Pre-existing personality traits of HNC patients
# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=12)</th>
<th>Citalopram (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean years)</strong></td>
<td>61.4</td>
<td>60.9</td>
</tr>
<tr>
<td><strong>Sex (% female)</strong></td>
<td>67</td>
<td>38</td>
</tr>
<tr>
<td><strong>Tumor type (% squamous)</strong></td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td><strong>Tumor Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III or IV (%)</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td><strong>Treatment Type (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>75</td>
<td>62</td>
</tr>
<tr>
<td>Radiation</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>33</td>
<td>30</td>
</tr>
</tbody>
</table>
Does the proposed research place the subject “at risk”.

Definition of risk: A subject is considered to be at risk if he may be exposed to the possibility of harm, whether physical, psychological, sociological, or other, as a consequence of any activity...
If risk is involved

Rights + welfare of subject
Methods of consent
Risks are outweighed by benefit either to self or society
Selection of subjects is equitable