State of Psycho-Oncology in cancer care: the science & the art.

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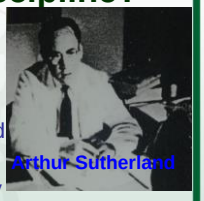
MONASH University

BACKGROUND

History of Psycho-oncology Why a distinct discipline?

- 1900-50's: Surgery, Radiation & Chemo developed
- 1960s: **Truth telling debates**
- 1970s: Strong consumer demand – breast cancer lobby
- Strong research from psychology
- **Need for a mainstream alternative to the un-proven therapies industry in cancer care**
- **Existential & spiritual challenges present a significant unmet need**


Arthur Sutherland

Cancer Facts

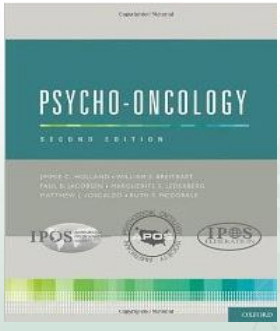
- Affects nearly 1/2 of population; 3/4 families
- A leading cause of death
- Survivorship challenges for >65%

- Life transition providing key opportunity
- Like a mid-life crisis for many!
- For advanced cancer, key interface with palliative care & bereavement

Cancer Fears

Holland, 1979

- Death
- Disfigurement
- Disability
- Discomfort – distress
- Dependency
- Disruption of relationships

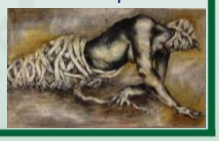


Oxford University Press 2015

Third edition of Jimmie Holland's classic textbook

Cancer Coping - influences

- Disease biology & its treatment
- **Prior adjustment: personality & coping style**
- Stage in life cycle: role / existential
- **Culture & religion**
- Concurrent stressors: financial / occupational
- **Support & family functioning**



Structure of this talk: Cancer Phases of Care

1. Prevention – screening, health promotion
2. Diagnosis – crisis, grief, threat
3. Treatment – disfigurement, burden
4. Post treatment – adaptation
5. Survivorship – sexuality, fertility, late effects
6. Recurrence – threat & grief
7. Advanced – existential / family
8. Bereavement – continuity of care

1. Prevention

(Screening & Health Promotion)

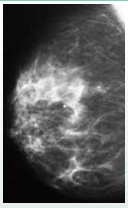
Risks & Cancer Prevention

- **Tobacco/ alcohol/ sun/ fiber/ exercise/ vaccine**
- **Smoking cessation**
  (>20% cessation >8 sessions)
  - **motivational counseling**,

Nicotine replacemt; Bupropion 14-16% abstinent; Varenicline 0.5mg 1mg 2mg 22% abstinent [warn dep]

- **teachable moments: surgery/dentistry**
- **public health initiatives**

Screening



- Mammography, PAP smear, Colonoscopy, skin checks & MoleMaps
- **Health beliefs**: perception of susceptibility, barriers, benefits. Impact of cultural beliefs. Economic & psychological barriers pertinent; physician knowledge.
- Minority populations & low socio-economic groups screen less; public health education challenge (Johansen et al, 2010).

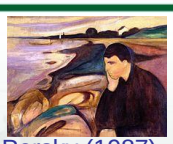
Genetic Counseling

- Risk pedigrees: cancers bilateral, multicentric, young age, atypical site or gender, multiple first degree relatives
- Counseling: surveillance; prophylactic surgery; prevention therapy
- Issues: intrusive anxiety; decision-making; family secrets & dynamics – guilt, denial;
- Children: Age of testing? Use of O/C? Age of reproduction & then prophylactic surgery?

Personality & Cancer

- 1984: Temoshock & Fox – Type C
- 1987: Shaffer's 35yr followup of 972 med students – "loners, non-aggressive, emotionally repressed" ⇧x15 cancer
- 1989: Todarello – alexithymia (no words…
- Issues: retrospectivity, older pt cohorts, self-blame & guilt. Danish studies better.
- **Today: personality not a cause of Ca.** [Risk taking, substance dep, occup expos]

Depression causing Cancer



- Positive: Old studies – e.g Persky (1987) 20yrs post MMPI, n2020 RR 2.3
- Negative: Kaplan (1988) n6801; Hahn (1988) n8932; Linkins (1988) n2501; Zonderman (1989) n2586;

  All nonsignificant

Today: depression not a cause of Ca

[but Obesity, smoking, alcohol, exercise]

Life Events & Cancer

- Problem of retrospective attribution
- Methodological problems with small cohorts
- Ewertz 1986: large Danish matched control cohorts – parental bereavement not associated with cancer
- Myth of stress causing cancer [Li, Cancer, 2002]
- **Today: stress not a cause of cancer**

Social Support & Mortality

- 1988 House: Social isolation as dangerous as smoking & high cholesterol
- 1987 Goodwin, 1989 Ramirez: single/divorced worsens cancer prognosis; marriage more protective for males
- **Today: human attachment reduces mortality**

Unmarried patient outcomes

- **Present late with metastatic disease** (Osborne et al, 2005)
- **Less likely to receive definitive anti-cancer therapy** (Wang et al, 2011)
- **More likely to die earlier** (Fossa et al, 2011; Sammon et al, 2012; Wang et al, 2011; Aizer et al, 2013)
- **Marriage as protective as chemo** (Aizer et al, 2013)

Cancer Survival & Group Therapy

Spiegel's 1989 group therapy study:

Inadvertent sampling bias likely (Fox BH, 1998)

- **NCI's SEER data: 32% of women with met ca live beyond 5 years**
- **2.8% of Spiegel's controls & 24% of group intervention arm were alive at 5 yrs**

Fawzy's 1993 melanoma study

Coyne, Stefanek & Palmer, 2007

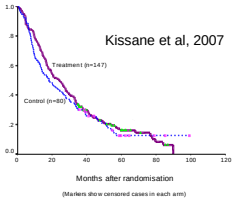
- **SEER data stage 1 melanoma: 92% 5-yr**
- **Fawzy's control arm: 72% survived 5 yrs**
- **Analyses not intention-to-treat**

Does Supportive-Expressive Group Therapy extend Survival?

3 replication RCTs of SEGT all failed to find a survival benefit but improved quality of life

- **Goodwin PJ et al., 2001: n = 235**
- **Kissane DW et al., 2007: n = 227**
- **Spiegel D et al., 2007: n = 125**

Power to detect 15% gain in survival



Replication of Fawzy's Psycho-educational intervention in melanoma

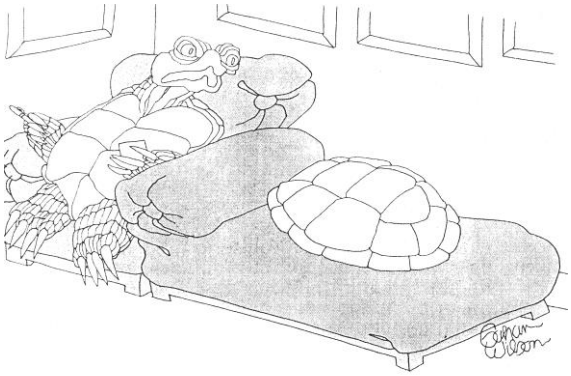
[Recruitment between 1999 & 2001] **Boesen et al.**

- **J Clin Oncol 2005, 23: 1270-7. n = 262 Reduced fatigue & improved mood**
- **J Clin Oncol 2007, 25: 5698-703. No survival benefit from intervention after 4-6 years.**

Non-participants (n = 137) had lower socio-economic status and a two-fold poorer survival.

Psycho-oncology & Cancer Survival Debate

- **Improved**: Spiegel 1989, Richardson 1990, Fawzy 1993, Ratcliffe 1995, Kuchler 1999, Andersen 2009 (not univariate)
- **No Change**: Linn 1982, Ilnyckyj 1994, Cunningham 1998, Edelman 1999, **Goodwin 2001, Kissane 2004, Spiegel 2007, Kissane 2007, Boesen 2007**.
- **Mechanisms**: Support, coping, psycho-neuroendocrinology, psycho-neuroimmunology, **behavioral-adherence**



"This is getting us nowhere!"

Did we get it wrong?

- **If marriage as a source of social support is protective……**

- **Inadequate power…….cohort of 2000?**
- **Wrong demographic…..single, separated, divorced, widowed……..not marrieds?**
- **Wrong clinical group…..depressed?**

Predictors of Shorter Survival

- Helplessness / hopelessness, Depression (DiClemente 1985; Goodkin 1985; Watson 2000 & 2005) – poor adherence to anti-cancer treatment

- Social deprivation (Boesen et al. 2007; Johansen, 2010) – underserved minority & low socio-economic communities

Meta-analyses of impact of depression on cancer mortality

- Chida et al, 2008: 15 studies of cancer patients, RR 1.08
- Satin et al, 2009: 25 studies, RR 1.25–1.39
- Pinquart & Duberstein, 2010: 76 studies (n= 177,000 patients) RR of 1.19

- Mechanisms: 1) not persevere with treatment; 2) more smoking & alcohol / obesity / reduced exercise; 3) physiological dysregulation of cortisol /melatonin; 4) reduced benefits from social support

SEGT & Depression prophylaxis

Kissane et al. 2007

- At their final assessment (closest to death), irrespective of time point, women who were depression-free at baseline fared better in SEGT in that they were more likely to remain depression free than controls (chi-square = 5.125, p=0.024, effect size = 0.20).

- SEGT both treated & prevented DSM-IV Depressive Disorders

2. Diagnosis

(Crisis, Grief, Threat)

Suffering

- **Threat to integrity of self**, loss, negative emotion, enduring and promoting helplessness (Eric Cassell 1982)

Common causes:

1. **Unrecognized depression;**
2. **Existential distress;**
3. **Poor symptom control;**
4. **Communication failure;**
5. **Fatigue &**
6. **Family dysfunction**

(Nathan Cherny 1994)

Existential Distress

Kissane, 2001, 2010

Challenge	Adaptation	Symptomatic
Death	Courage	Fear
Loss	Sadness	Complex grief
Aloneness	Accompanied	Isolated
Freedom	Acceptance	need Control
Meaning	Fulfilled	Demoralized
Dignity	Sense of worth	Worthless
Mystery	Reverence	Spiritual doubt

Existential Distress & Psychiatric Disorders

• Death	anxiety, pain
• Loss	depression
• Aloneness	relational conflict/marital
• Relationship	family dysfunction
• Freedom & control	phobic, OCD, substance abuse
• Meaning	demoralization, depression
• Dignity	adjustment disorders
• Mystery	anxiety & depression, adjustment disorder

Kissane, DW (2012). The relief of existential suffering. *Archives of Internal Medicine*, *172*(19), 1501-1505

‘THE COURAGE TO BE’

Paul Tillich, 1952

- **‘Man’s power of life is his freedom and the spirituality in which vitality and intentionality are united.’**
- **Courage to be part of the whole, the community**
- **Courage to be oneself, self-affirming ..... the unique person**
- **Courage to fear, to doubt, to despair**

Epidemiology of Psychiatric Disorders in Oncology

- Derogatis’ PSYCOG (1983): DSM-III
  - 11% prior psych diagnosis
  - 89% response to cancer
- **47% Psychiatric Disorder Rate**
  - 13% major depression
  - 68% adjustment disorder (anx, dep)
  - 8% delirium
- Pain associated with twice the rate of psychiatric disorders

2a. Epidemiology of psychiatric disorders

Prevalence psychiatric disorder

by meta-analysis

International literature reviews
based on structured clinical interviews (DSM/ICD) show the following prevalence rates for affective and anxiety disorders:

Affective Disorders: **11%** (95%CI 8.1–15.1)*

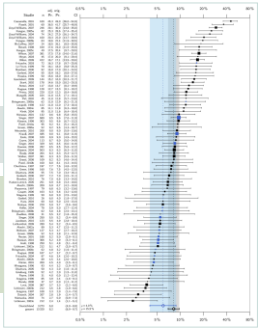
Anxiety Disorders: **10%** (95%CI 6.9–14.8)

Mental comorbidity in palliative care:

Depression: **16.5%** (95% CI 13.1–20.3)**

Adjustment Disorders: **15%** (95% CI 10.1–21.6)

Anxiety Disorders: **10%** (95% CI 6.8–13.2)



*Vehling, Mehnert et al., PPmP (2012), **Mitchell et al., Lancet Oncology, 2011

Study centers across Germany

Multisite Psychooncology-Epidemiology Study

Mehnert, Anja & colleagues

Universitätsklinikum Hamburg-Eppendorf
Prof. Dr. Dr. Uwe Koch, PD Dr. Anja Mehnert
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PD Dr. Monika Keller
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Prof. Dr. Elmar Brähler
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Prof. Dr. Dr. Martin Härter
Universitätsklinikum Hamburg-Eppendorf:
Prof. Dr. Karl Wegscheider

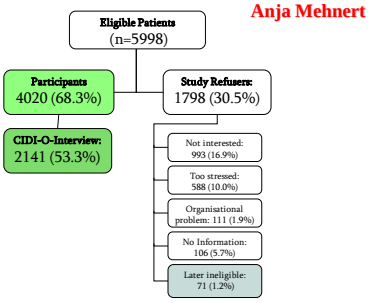
Inpatient 40%; Outpatient 40%; Rehabilitation 20%

Tumors sampled proportional to prevalence nationally
Initial screening, then CIDI interviews [100% if screen pos & 50% random sample if screen neg]

Random sample & CIDI interviews

German Multisite Psychooncology-Epidemiology Study

Anja Mehnert



Prevalence of Psychiatric Disorder (CIDI-O) I

Psychiatrisches Störungsbild	Diagnose not present n	%	Diagnose present n	%
Organische. einschließlich symptomatischer psychischer Störungen (F00-F09) **Organic disorders**				
Irgendeine organische psychische Störung				
Lebenszeitprävalenz	2023	94.5	118	5.5
12-Monats-Prävalenz	2044	95.5	97	4.5
1-Monats-Prävalenz	2079	97.1	62	2.9
Psychische und Verhaltensstörungen durch psychotrope Substanzen (F10-F19) **Substance use disorders**				
Missbrauch oder Abhängigkeit durch irgendeine Substanz (Alkohol oder Tabak)				
Lebenszeitprävalenz	1647	76.9	494	23.1
12-Monats-Prävalenz	1948	91.0	193	9.0
1-Monats-Prävalenz	2023	94.5	118	5.5 #
Affektive Störungen (F30-F39) **Affective Disorders**				
Irgendeine affektive Störung				
Lebenszeitprävalenz	1632	76.2	509	23.8
12-Monats-Prävalenz	1807	84.4	334	15.6
1-Monats-Prävalenz	1959	91.5	182	8.5 #

Prevalence of Psychiatric Disorders (CIDI-O) II

Psychiatrisches Störungsbild	Diagnose not present n	%	Diagnose present n	%
Neurotische. Belastungs- und somatoforme Störungen (F40-F48)				
Irgendeine Angststörung **Anxiety Disorders**				
Lebenszeitprävalenz	1559	72.8	582	27.2
12-Monats-Prävalenz	1745	81.5	396	18.5
1-Monats-Prävalenz	1851	86.4	290	13.5 #
Posttraumatische Belastungsstörung (PTSD) **PTSD**				
Lebenszeitprävalenz	2018	94.2	123	5.7
12-Monats-Prävalenz	2073	96.8	68	3.2
1-Monats-Prävalenz	2088	97.5	53	2.5
Irgendeine Somatoforme Störung **Somatoform disorder**				
Lebenszeitprävalenz	1688	78.8	453	21.2
12-Monats-Prävalenz	1920	89.7	221	10.3
1-Monats-Prävalenz	2022	94.4	119	5.6

German psycho-oncology prevalence of psychiatric disorders

Mehnert et al, unpub

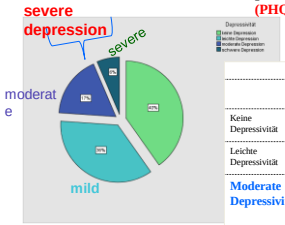
Type of Cancer	% Current Mood disorder	% Current Anxiety disorder	% Current Adjustment disorder
BREAST	11.1%	19.5%	15.5%
PROSTATE	3.2%	5.6%	5.1%
LUNG	6.2%	8.3%	6.7%
BOWEL	6.1%	11.4%	9.5%

Need differs by cancer type

Prevalence of Psychiatric Disorder by Screening

Mehnert et al, unpublished

23% with moderate or severe depression

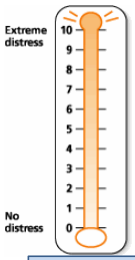


Depressivität (PHQ-9)

P<.001, φ = .09

	Versorgungsbereich		
	Stationär	**Ambulant**	**Rehabilitation**
Keine Depressivität	41%	44%	34%
Leichte Depressivität	35%	35%	39%
Moderate Depressivität	**17%**	**15%**	**21%**
Schwere Depressivität	**7%**	**6%**	**6%**

2b. Distress Screening



DISTRESS

Definitions: anguish, sorrow, pain, heartache, misery, strain or worry

Distress call: in danger and needing help

Non-stigmatizing word is easier to acknowledge

Roth AJ, Kornblith AB, et al. **Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study.** Cancer. 1998 82(10):1904-8.

Jacobsen PB et al. **Screening for psychologic distress in ambulatory cancer patients.** Cancer. 2005 103(7):1494-502.

IPOS International Standard of Quality Cancer Care *2010*

1. **Quality cancer care** must integrate the **psychosocial domain** into routine care;

2. ***Distress should be measured as the 6th Vital Sign*** after temperature, blood pressure, pulse, respiratory rate and pain

Details on www.ipos-society.org

INTERNATIONAL PSYCHO-ONCOLOGY SOCIETY IPOS 30 years

uicc global cancer control — Union for International Cancer Control

Dr Eduardo Cazap, UICC President
Shenzhen, China, August 2010

"We expect that recognizing distress as the 6th vital sign will improve the treatment of cancer patients, improve outcomes for cancer patients, and improve the effectiveness of cancer care systems around the world"

WORLD CANCER DECLARATION 2013

The World Cancer Declaration calls upon government leaders and health policy-makers to significantly reduce the global cancer burden, promote greater equity, and integrate cancer control into the world health and development agenda.

OVERARCHING GOAL:

There will be major reductions in premature deaths from cancer, and improvements in quality of life and cancer survival rates.

BY 2025:

Target 08 - Effective pain control and distress management services will be universally available

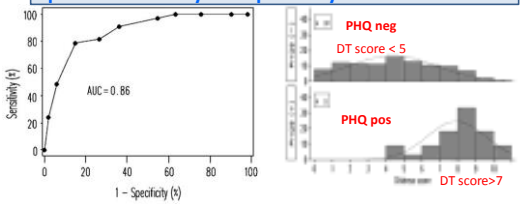
uicc global cancer control

WWW.UICC.ORG/WORLD-CANCER-DECLARATION

Sensitivity and specificity of the Distress Thermometer for depression in cancer patients

Mark T. Hegel, et al and Tim A. Ahles. Psycho-Oncology. 2008 Jun; 17(6): 556–560.
doi: 10.1002/pon.1289

The single-item DT performs satisfactorily relative to the PHQ-9 for detecting depression in cancer patients. A cutoff score of 7 on the DT possesses the optimal sensitivity and specificity characteristics.



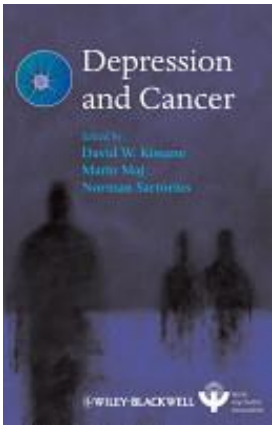
Staffing profile to deliver services

- **Inpatient services aim to reach:**

Psychiatry: 10% of patients
Psychology: 10%
Social work: 50% +

- **Outpatient services aim to reach:**

Psychiatry: 5% of patients
Psychology: 15% of patients
Social work: 35% plus



Commissioned by World Psychiatric Association;

David W. Kissane, Mario Maj, Norman Sartorius (Eds)

John Wiley & Sons, 2011 - 258 pages

Cancer Depression & Contributory Factors

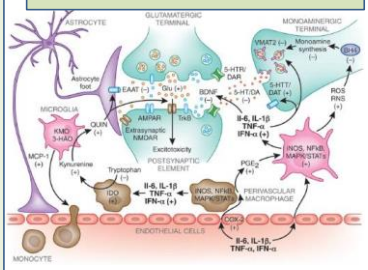
- **Gender**: major depression in breast cancer (early 10%, advanced 7%); prostate cancer 4%; wives 10%; (Kissane 2004)
- Advanced disease, Neurological disorder, Pain & poor symptom control, metabolic, & endocrine
- **Medications**: interferon, steroids, interleukin-2, some chemo [Vincristine, Vinblastine, Procarbazine L-Asparaginase], antihypertensives [propanolol, reserpine, methyl dopa], antibiotics (amphotericin)
- **Specific cancers**: cytokines from pancreas; lymphoma; oat cell; paraneoplastic syndromes

CYTOKINES AND DEPRESSION

Cytokines are cell signal molecules that communicate between cells to modify their behaviour, induce inflammatory responses, and mobilize defences.

Cascade of tiny proteins secreted by cancer cells (e.g., interferon, interleukin, tumour necrosis factors and growth factors) which can cross the blood brain barrier and interact with the mood regulating limbic circuits of the brain.

Depression as an inflammatory response



Ebrahimi, et al, Cancer, 2004; Musselman, et al.: AJP 158.1252-1257 Aug 2001

Cancers with cytokine storms

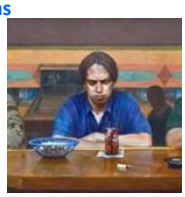
- **Pancreatic cancer**
- **Lung cancer**
- **Lymphoma**
- **Breast, ovarian**
- **Renal**

- **Metastatic cancers more so than early stage**
- **Chronic or recurrent storms**

Organic affective syndrome

Notion of Depression occurring in medically ill

Not a simple matter of 'coping'



Prophylactic Antidepressant Against Interferon-induced Depression

Patients with melanoma receiving Interferon were randomized to Paroxetine vs. Control

Patients received 10-40mg/day Paroxetine for 2 weeks prior to, and 12 weeks after interferon treatment.

Paroxetine significantly reduced the incidence and severity of depression. 11% depression in Paroxetine group vs. 45% depression in control group. Musselman, et al. NEJM, 2001

Endicott Substitution Criteria

J Endicott, Cancer, 1984

Somatic Symptoms	Substitution Symptoms
• change in weight or appetite	• depressed appearance
• sleep disturbance	• social withdrawal or decreased talkativeness
• loss of energy or fatigue	• brooding, self- pity, or pessimism
• difficulty in thinking or concentrating	• lack of reactivity in situations that would normally be pleasurable

Inclusive, exclusive or substitutive approach

Suicide & Cancer

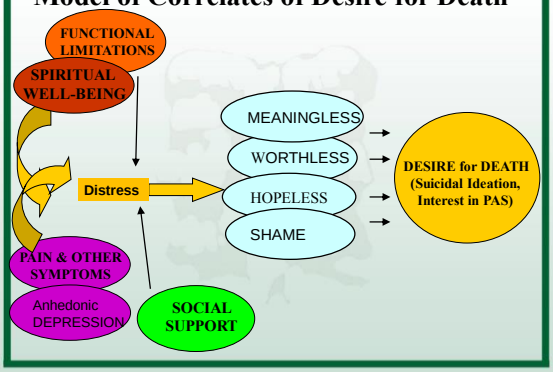
- Rates slightly increased (Louhivouri 1979; Fox 1982; Bolund 1985)
- Risks: pain, poor symptom control, debility, social isolation, delirium, depression, demoralization, P.H. psychiatric disorder

Recklitis CJ, et al J Clin Oncol 24: 3852-7, 2007
Schairer C, et al. J Natl Cancer Inst. 98: 1416-9, 2006

Sites of Cancer Associated with Suicide

Studies	Primary Sites
UNITED STATES	
Weisman	Oral, urogenital
Farberow et al.	Tongue, larynx, lung
Farberow et al.	Lymphoma, leukemia (> 45 years)
Breitbart	Lung, bronchus, trachea, intestine (45-65 years), pharynx, larynx (> 65years)

Model of Correlates of Desire for Death



Euthanasia and Depression

A prospective Dutch study in 138 terminally ill cancer patients to examine the association between depression and **request for euthanasia**

Results:

- **22% of patients requested euthanasia;**
- **23% were depressed at baseline;**
- **44% of the depressed patients requested euthanasia compared to 15% of the non-depressed.**
- **The rate of request for euthanasia for patients with depression was 4.1 times greater that that of patients without depression.**

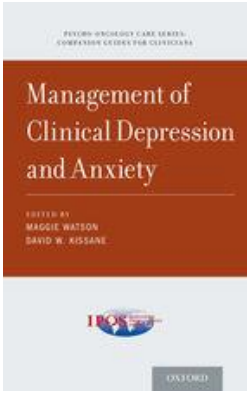
Van der Lee, et al, JCO, 2005

Changed Interest in Life-sustaining Treatments

- Treatment of depression shifts interest from 6 /14 to 10 / 14 potential medical therapies
  - Ganzini, 1994
  - Hooper, 1996
  - Rosenfeld, 1996

Physician-assisted Suicide & Euthanasia

- Rational suicide if sensible reasons in keeping with fundamental interests serve the good (Mayo 1996)
- 3 forms: Altruistic, avoiding evil, promoting good in self (Motto 1980)
- Most requests for PAS in palliative care are searches for help to cope better / not be abandoned
- Important to recognize & treat depression



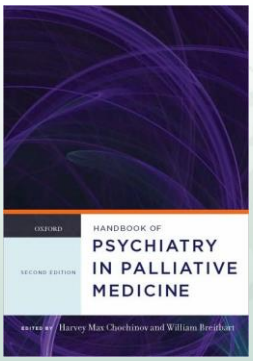
IPOS Psycho-Oncology Care Series:

Companion Guides for Clinicians,
Oxford University Press, 2017

MANAGEMENT OF CLINICAL DEPRESSION AND ANXIETY

Edited by
Maggie Watson
David W Kissane

Discounted for IPOS members

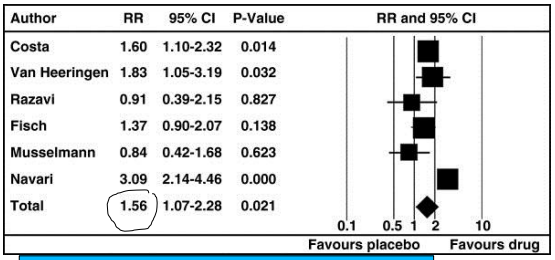


Second Edition of Chochinov & Breitbart's Handbook of Psychiatry in Palliative Medicine, Oxford University Press, 2009

3. Treatment

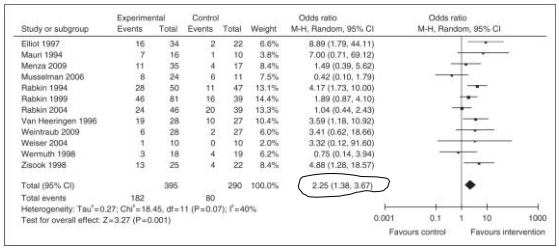
a. Do we treat depression well?

Meta-analysis of efficacy of anti-depressants in cancer care
N=563 patients; effect size using Risk Ratio in Forrest plot = 1.56 [95% CI: 1.07- 2.28; p= 0.021]



Laoutidis and Mathiak BMC Psychiatry **2013**, 13:140
http://www.biomedcentral.com/1471-244X/13/140

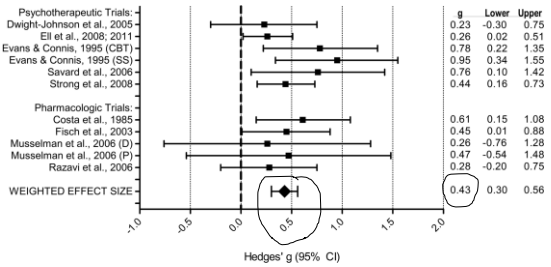
Forest plot of response to antidepressant treatment in palliative care at 6–8 weeks



Rayner L et al. Palliat Med 2010;25:36-51

PALLIATIVE MEDICINE

Combined psychotherapeutic and pharmacological therapies reduce depressive symptoms in cancer care
N= 1362 mixed cancers g=0.43 p<0.001



Hart SL, …Stanton AL. Meta-Analysis of Efficacy of Interventions for Elevated Depressive Symptoms in Adults Diagnosed With Cancer. J Natl Cancer Inst **2012**;104:990–1004

Unrecognised & untreated depression in cancer care

DW Kissane, Lancet Psych 2014

Consequences of depression:

- Increased **mortality** from cancer – **up 17% in meta-analysis of 76 studies** (176,863 patients) by Pinquart & Duberstein (2010)
- **Higher suicide rates** in cancer (Hem et al, 2004)
- **Higher requests for euthanasia** (van der Lee et al, 2005)
- Three-fold **reduced adherence** to anti-cancer treatments (DiMatteo et al, 2011)

Routine screening (HADS) confirmed by SCID (Walker et al, 2014):

- 21,000 outpatients screened over 3 yrs
- Prevalence lung ca (13.1%); gynaecological ca (10.9%); breast ca (9.3%); colorectal (7%); lowest in genitourinary ca (5.6%).
- More prevalent in younger, socially deprived & female patients.
- **73% of depressed patients not in receipt of treatment**

SMaRT Oncology-1 trial

Strong, Sharpe et al, Lancet 2008

Collaborative care treatment program for patients with major depression in cancer.

Nurse practitioners, supervising psychiatrists and GPs formed the collaborative care team.

•Proof of principle as an efficacy study: 200 cancer outpatients with prognosis >6 months. The difference in mean Symptom Checklist-20 depression score, between those who received the intervention and those who did not, was 0.34 (95% CI 0.13-0.55).

•**Effect size = 0.43 (0.16–0.71).**

Symptom Management Research Trials (in Scotland)

SMaRT Oncology-2 trial

Sharpe et al, Lancet 2014

Collaborative care treatment program for patients with major depression in cancer.

Nurse practitioners, supervising psychiatrists and GPs formed the collaborative care team delivering depression care (DC). GPs delivered usual care (UC)

Patients identified by screening (HADS followed by SCID)

500 patients enrolled (2008-2011) across 3 sites in Scotland (Glasgow, Edinburgh & Dundee). Outcome 50% reduction on SCL-20 over 1 year. **Effectiveness RCT**

Randomization in 1:1 ratio to collaborative care by team or usual care by GP

Responders to treatment: 143/231 **(62%) in DC** and 40/231 **(17%) in UC**

Absolute difference 45% (95% CI 37-53), adjusted odds 8.5 (95% CI 5.5-13.4), p<0.001

Treatment intensive: **dose increases in ADs, 10 sessions of therapy, drugs changed if resistant, seen by psychiatrist; these changes were not seen in UC.**

SMaRT Oncology-3 trial

Walker…Sharpe, Lancet Oncol 2014

- Multicentre lung cancer trial in Scotland using the collaborative care model for treatment of depression
- 142 pts randomized to 'depression care' or 'usual care'

- Standardized mean difference in reduction in SCL-20:

  -0.62 (95% CI -0.94 to -0.29)

Messages

- **May be a lot of unrecognised & untreated depression**
- **Combination psychotropic & psychotherapy as treatment**
- **Intensive treatment escalation may be needed**
- **Multidisciplinary psycho-oncology teams help a lot**

3b. Any traps in treating depression?

Tamoxifen & P450 system

- **Tamoxifen → 4-hydroxy-tamoxifen (endoxifen)**
- **If CYP 2D6 poor metabolizer genotype** (Jin 2005), **survival outcome poorer.**
- **Tamoxifen + Paroxetine → poorer survival** (Stearns, JCO, 2003)

- **Potent** CYP2D6 Inhibitors: paroxetine, fluoxetine, sertraline, buproprion
- **Minimal** CYP2D6 Inhibition: venlafaxine
- **No** CYP2D6 Inhibition: citalopram (Lash, BritJCan, 2008), mirtazapine

Abiraterone & P450

- CYP2D6: paroxetine, sertraline, fluoxetine will all compete with Abiraterone
- Safe antidepressants: citalopram, venlafaxine, mirtazapine

- CYP3A4 Inducers: rifampicin, ketoconazole, nefazodone, protease inhibitors

Irinotecan & SSRI^{s}

- **Hypericum (St. John's wort) induces P450 CYP3A4 with deleterious outcome in colon ca when Irinotecan used.** (Mathijssen, 2002)

- **Inhibitors of CYP2B6 (desipramine, paroxetine, and sertraline) increase level of Irinotecan, causing severe diarrhea & rhabdomyolysis** (Richards et al, 2003)

Drug interactions with SSRIs, SNRIs, Linezolid (MAOI antibiotic),Tramadol, Opioids, Methadone, 5HT3 antagonist anti-emetics (Ondansetron, Granisetron) [Lee et al, Psychosomatics, 2009; Takeshita & Litzinger, 2009]

Symptoms & Management in Serotonin Syndrome:

Mild	Moderate	Life Threatening
Mydriasis Shivering Sweating Tachycardia (mild)	**Altered Mental Status** (agitation, disorientation, excitement) **Autonomic Hyperactivity** (rigidity, tachycardia, hyperthermia of >40°C) **Neuromuscular Abnormalities** (tremor, clonus, hyperreflexia)	Delirium Hypertension Hyperthermia Muscle rigidity Tachycardia

Management stages:

Observe for at least 6 hrs
Benzodiazepines

→ Admit to hospital
Cardiac monitoring
Cyproheptadine

→ Intensive care unit
Esmolol or nitroprusside
Cooling measures,
Sedation, SkM paralysis, ventilation

[Kim & Fisch, 2006]

Demoralization Syndrome

Kissane et al, 2001, 2004; Mehnert, 2011

- Low morale, poor coping
- Loss of meaning, pointlessness
- Helpless – hopeless
- Social isolation
- Desire to die

High demoralization, low depression in 7-14%

Religion, spirituality protects; substance dependence worsens

Post Traumatic Stress Disorder

- Intrusive thoughts, avoidance, numbing or arousal
- Symptom prevalence: 7% - 62%
- Disorder prevalence: 4% - 17% survivors
- Therapies: CBT, Behavioral, SSRI & anti-anxiety
- Telephone-based CBT reduced PTSD in BMT subjects [**DuHamel et al, JCO, 2010**]

3c. Delirium

Delirium

- Prevalence: **33% inpatient referrals** (Massie 1979) rising to 62% palliative care (Pereira 1997)

- **Hyperactive & Hypoactive**
- Seek causes; safety & support
- Haloperidol 0.5 - 1.0mg po/iv hourly; olanzapine 2.5mg; risperidone 1-3mg 12 hourly; chlorpromazine
- Lorazepam 0.5 - 2.0mg 1-4 hourly; clonazepam 0.5 - 2mg

Occurrence, Course, Outcome of Delirium in Advanced Cancer Patients

Terminal delirium seen in 88% of deaths

An average of 3 etiologic factors for delirium

Delirium is reversible in < 50% of terminally ill

Psychoactive medications (i.e. opioids) and dehydration associated with reversibility

Hypoxic encephalopathy and metabolic factors were associated with irreversibility

Patients with delirium had poorer survival rates than controls (p< .001) [Lawlor,P. et al 2000]

Multi-organ failure in advanced ca suggests delirium will be a terminal event [Friedlander & Kissane, 2005]

Chemotherapies and Other Medications That Can Cause Delirium

L-Asparaginase
Bleomycin
Carmustine (BCNU)
Cisplatin
Cytosine arabinoside (ara-C)
Fludarabine
Fluorouracil
Interferon
Interleukin
Ifosfamide
Methotrexate
Prednisone
Procarbazine
Vinblastine
Vincristine

Opioids
Corticosteroids
Acyclovir (I.V.)
Anticholinergic agents
Antiemetics
Histamine blockers
NSAIDs
Beta Blockers
Sedatives
Hypnotics
Antidepressants
Psychostimulants

Opioids and Delirium

- **Most patients on stable (even high) doses of opioids do not develop delirium.**
- **Highest risk of opioid-induced delirium is during rapid dose escalation, particularly intravenously.**
- **Risk factors include older age, renal or liver impairment, hypothyroidism, dementia**
- **Accumulation of toxic metabolites (e.g. morphine-6-glucuronide) managed by opioid rotation**

Kornick, et al, Pain, 2003

Ifosfamide-induced Encephalopathy

- **10-15% of patients treated with ifosfamide (a common alkylating agent) develop delirium**
- **Accumulation of chloracetaldehyde, a toxic metabolite of ifosfamide closely related to chloral hydrate, is the likely cause**
- **Ifosfamide-related delirium is often resistant to control of symptoms with neuroleptics**
- **Methlylene Blue (1-2mg/kg) via slow infusion may be effective in the management, both as prophylaxis or treatment of delirium**

Park, et al. 2005

Clinical trials of delirium treatment

- Haloperidol & Chlorpromazine effective in improving hyperactive & hypoactive delirium in AIDS, Lorazepam not [Breitbart et al, 1996]
- Olanzapine effective in advanced Ca [Breitbart et al, 2002]; age>70 yrs lowers MDAS response to 40% cf to 90% for younger patients.
- Risperidone equal in effectiveness to haloperidol [Han and Kim, 2004]
- Cochrane review: only neuroleptics help delirium [Lonergan et al, 2007]
- NB - Black box warning on neuroleptics

Delirium in the ICU

- Dexmedetomidine (Precedex 100 mcg/ml) 1mcg/kg loading dose over 10 mins; alpha$_2$ adrenergic agonist acts on locus ceruleus; 2-hr half-life; P450 2A6 metabolism; sedative with less respiratory depression; s/e on BP & bradycardia

- Propofol (Diprivan) sedative/anesthetic; acts on GABA receptor & Na channel; short half-life

Black box warning on neuroleptics

- 17 trials (5,106 patients): 1.6 fold increase in mortality [Schneider et al, JAMA, 2005]
- Elderly with dementia: 23,000 pts; higher deaths with typical than atypicals [Wang et al, NEJM, 2005]
- Causes:
  - Prolonged QTc interval: cardiac event
  - Stroke
  - Diabetic ketoacidosis
- Cardiology consult: Aripiprazole minimal effect on QTc, weight, glucose, lipids [Straker et al, Psychosomatics, 2006]

Paraneoplastic Syndromes & S.C.L.C. (also breast, ovarian, Hodkin's)

- Cerebellar degeneration: ataxia, nystagmus, dysarthria
- Brain stem encephalopathy: ataxia, cranial N^s, corticospinal
- Limbic encephalopathy: depression, cognitive change
- Optic neuritis: visual loss, myoclonus

All progress to dementia.

3d. Counselling & Psychotherapy

Engage the person with questions & listening

"Although you've yet to try your water or even order an entrée, how is everything?"

Eclectic Approach to Counseling

- **Grief therapy**, **Existential Px**, **Supportive-expressive** – universal
- **CBT** – fear, existential uncertainty, behavioral
- **IPT** – grief, role, transition, interpersonal
- Newer: meaning-centered, dignity-conserving, narrative therapies
- **Couple & Family therapy** approaches

Meta-analyses of Psychotherapy in Psycho-oncology

- **Meyer & Mark, 1995: n=45 studies; Px effective, but overall effect size small; d=0.24**
- **Devine & Westlake, 1995: n=116 studies; psycho-educational models have large effect size; d=1.0**
- **Sheard & Maguire, 1999: quality of design;**

n=19 anxiety d=0.42; n=20 depression d=0.36;

n=4 CBT for distress (d=0.94 anx & d=0.84 dep);

group ≥ individual; skilled therapists achieve briefer i/vs, but length (dose) relevant

Effects of Psycho-Oncologic Interventions on Emotional Distress and Quality of Life in Adult Patients With Cancer: Systematic Review and Meta-Analysis
Faller et al, J Clin Oncol 31:782-793, 2013

- **198 studies (covering 22,238 patients) that report 218 treatment-control comparisons.**
- **Significant small-to-medium effects were observed for individual and group psychotherapy and psychoeducation.**
- **These effects were sustained, in part, in the medium term (≤ 6 months) and long term (>6 months).**
- **Studies that preselected participants according to increased distress produced large effects at post-treatment.**
- **A moderator effect was found for "duration of the intervention," with longer interventions producing more sustained effects.**

Psychotherapy works

Conquer Fear

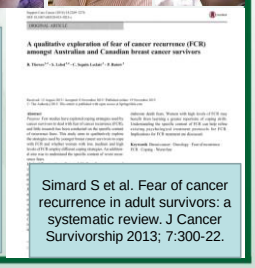
- Realistic
- Metacognitive
- Acceptance

Cognitive-Existential Group Therapy

Kissane et al (1997) Themes & techniques. Psycho-Oncology 6: 25-33

RCT outcomes – Psycho-Oncology. 2003 Sep;12(6):532-46

Survival outcome - J Clin Oncol. 2004 Nov 1;22(21):4255-60

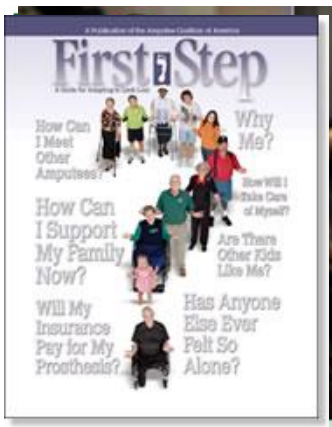


A qualitative exploration of fear of cancer recurrence (FCR) amongst Australian and Canadian breast cancer survivors

Simard S et al. Fear of cancer recurrence in adult survivors: a systematic review. J Cancer Survivorship 2013; 7:300-22.

LIMB AMPUTATION

- Grief therapy
- CBT
  - Stump is ugly!
  - People will stare!
  - New self: 'damaged' versus 'disability'
  - Mastery over functional skills
- Amputee's groups & Amputee's coalition
  - We can cope!



LYMPHEDEMA

GOAL: Manage disability, Grieve & Get on with life

Grief therapy
- **Body image work**

CBT
- **Behavioral approaches to wrapping & sleeves**
- **Cognitive approaches to self image, personhood, priorities in life – integrate a self schema that accepts disability**

Dignity therapy

Chochinov et al, 2005

- **Life story**
- **When most alive?**
- **Family to remember?**
- **Key roles?**
- **What accomplished?**
- **Hopes for family?**
- **What do you want to pass on?**
- **Guidance to others?**
- **Comfort to others?**

***Chochinov et al, Lancet Oncol* 2011; 12: 753–762**

Meaning-centered group psychotherapy for patients with advanced cancer

TOPICS

1. **Concepts & sources of meaning**
2. **Cancer & meaning**
3. **Story of your life**
4. **Finiteness of life**
5. **Responsibility, creativity & deeds**
6. **Nature, art & humor**
7. **Goodbyes & Hopes for future**

- **7 X 90-min groups**
- **Psycho-educational**
- **Based off Frankl's logotherapy**
- **Improved spiritual wellbeing & sense of meaning; reduced anxiety; reduced desire-for-death.**

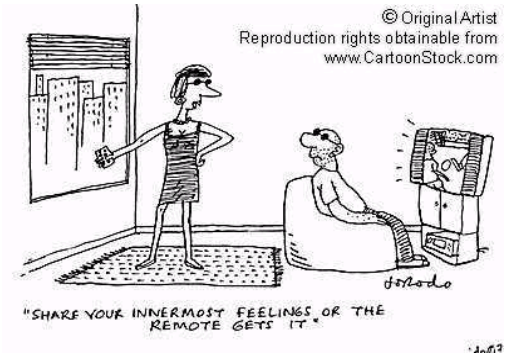
Breitbart et al, Psychooncology, 2010
- JCO 2012, 2014

Intimacy-Enhancing Couple Therapy

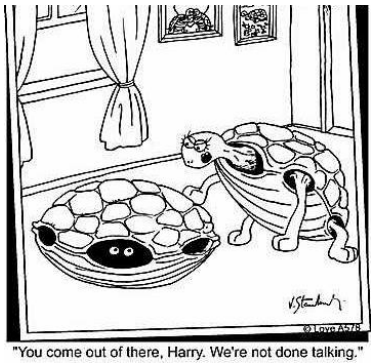
Manne, Kissane, et al, 2011

Outcome	IECT arm	Control	T-value(95%CI)	Significance
Interaction effects at 1SD below the mean				
Self-disclosure	15.1 (patient)	10.7	3.5 (1.9, 6.8)	0.0008
Perceived partner disclosure	14.6 (patient)	10.4	3.3 (1.7, 6.8)	0.0017
Perceived partner responsiveness	17.2 (patient)	15.8	3.3 (0.1, 2.7)	0.0341
Mutual constructive communication	32.3 (partner)	25.7	3.7 (3.0, 10.1)	0.0005
Intimacy	3.7 (partner)	3.0	3.4 (0.3, 1.1)	0.0011

Couples pattern: Pressure withdraw



More pressure



"You come out of there, Harry. We're not done talking."

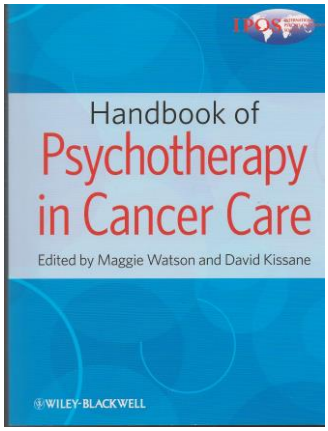
Criticism

May 2011

21 chapters

TI Zaider & DW Kissane

Ch 14
Couples Therapy
In Advanced
Cancer



RCT of Family Therapy in advanced cancer on "Prolonged Grief Disorder" Kissane et al, JCO 2016

CGI[a] Caseness	Time	Standard Care % (n/total)	FFGT 6-session % (n/total)	FFGT 10-session % (n/total)	GEE effects[b]
	Baseline	CGI data not collected pre-death			
	6 months bereavement	19.3 (11/57)	12.3 (13/106)	8.9 (9/101)	Treatment main effect Wald Chisq = 8.31, df = 2, p = 0.016
	13 months bereavement	15.5 (13/84)	12.1 (15/124)	3.3 (4/122)	

[a]CGI caseness applied criteria for Prolonged Grief Disorder. [b]Test statistics were based on a GEE model of CGI caseness as a function of 5 covariates: study stratification factors (site and family type), treatment assignment, time (e.g., 6 months vs. 12 mos), and a fifth covariate of a treatment by time interaction. The Wald Chi-square statistics were from the Wald test for the treatment by time interaction.

Special Issues in Psycho-oncology

- Needle phobia: relⁿ Rx & desensit ᴺ
- Conditional nausea : syst. desensit ᴺ (ondansetron & dexamethasone)
- Anorexia cachexia: megestrol, steroids, mirtazapine
- Pain: meaning / compliance
- Phantom limb / Neuropathic: tricyclics, gabapentin, lyrica

Psychopharmacology in Cancer

- **Co-analgesic effect from NA & 5HT mixed: Mirtazapine, venlafaxine, tricyclics**
- **Hot flashes – Venlafaxine** [Loibl et al, 2007; Buijs, 2009]
- **Antinausea benefit with HPL, Olanzapine** [Critchley et al, 2001; Tan et al, 2009]
- **Fatigue helped by Methylphenidate** [Minton et al, 2008] **or Buproprion** [Cullum et al, 2004; Moss et al, 2006]
- **Seizures: Citalopram least effect on threshold**
- **Pruritis: Mirtazapine** [Davis, 2003; Demierre, 2006]
- **Select benzodiazepines by half-life need**
- **Antidepˢ do not cause cancer** [Haukka, 2009]

Steroids in oncology

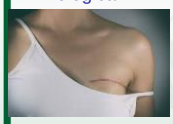
- Anti-emetics; restore BBB; vascular permeability; bone pain; well-being
- Neuropsychiatric side-effects in 5-10% clearly dose related (Stieffel et al, 1989) – insomnia, hypomania, depression, agitation & psychosis
- Treat - Lower steroid dose
- Concomitant neuroleptic – olanzapine 2.5-5mg qhs; quetiapine 25-200mg qhs

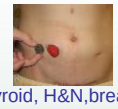
5. Survivorship

(sexuality, fertility, late effects; neurocognitive)

Psychological Morbidity in Survivors

- Biological
  - body image change
  - sexual dysfunction
  - infertility
  - secondary cancers: thyroid, H&N,breast
  - cardiac disease; chol & CAD





- Psychological
  - existential uncertainty, fear
  - vulnerability, control
  - somatization
- Social
  - job insecurity
  - life insurance
  - social rejection

Childhood Cancers

- Leukemia 31%, CNS 18%, lymphoma 12%, neuroblastoma 8%, sarcoma 7%, Wilm's 6%, bone 5%, germ cell 3%, retinoblastoma 3%
- Survival around 70%

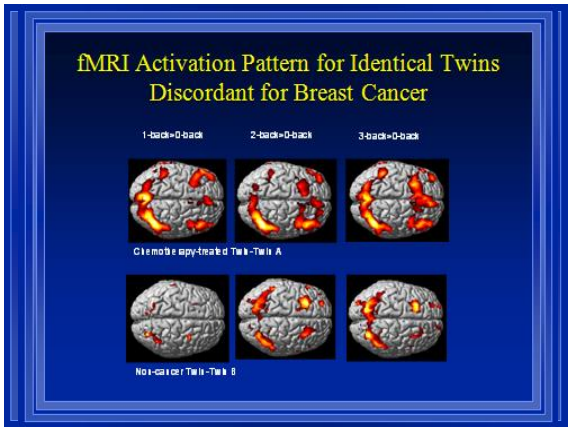
  Late effects impact hugely, including radiotherapy effects.
- Family disruption & support
- Survivorship care plans

Neurocognitive Research Program

- Chemotherapy-induced cognitive changes
  - Direct neurotoxicity
  - Immunologic inflammatory response
  - Microvascular injury

Control cog 11-12% decline

Study	n	Chemo	Time	%Cog-ve
Wieneke	28	CMF/CAF	6 month	75%
Ahles	35	CMF/CAF	10 yrs	34%
Brezden	71	CMF/CEF	2mo/2yr	48%/50%
VanDam	70	FEC/CTC	2yrs	32%
Schagen	39	CMF	2yrs	28%



Apolipoprotein E Gene & Chemotherapy-induced Cognitive Decline (Ahles 2003)

- Polymorphic APOE gene: 3 common alleles
- APOE ε2, ε3, ε4
- ε4 allele associated with Alzheimer's

Cog domain	ε4+ve(n17)	ε4-ve(n63)	P-value
Verbal learning	-0.20(1.2)	-0.03(1.0)	0.48
Visual memory	-0.30(1.1)	+0.04(0.8)	0.03**
Psychomotor f	-0.24(0.8)	+0.05(0.7)	0.08
Spacial ability	-0.38(1.2)	-0.13(1.0)	0.05**

Cognitive rehabilitation

- Ahles, Root, Ryan, JCO 2012: subgroup of patients is vulnerable to post-treatment cognitive problems.
- Models of aging important
- Cognitive training: e.g. Lumosity programs
- Root et al, 2015: attentional dysfunction may contribute to subjective and objective memory complaints in breast cancer survivors.
- Exercise studies

EXERCISE

- Courneya KS, 2003 Beneficial effects
- N = 301 breast cancer pts: RCT of supervised exercise of a standard dose of 25-30 min of aerobic exercise, a higher dose of 50-60 min of aerobic exercise, or a higher dose of 50-60 min of combined aerobic and resistance exercise. (Courneya et al 2015)

Exercise during chemotherapy to counter fatigue & promote wellness

6 & 7 Recurrence & Advanced Cancer

(threat & grief; existential & family)

Palliative Care – Family-centered

- Truth telling & transition to supportive care
- **Prognostication**: 2x to 5x error [Christakis, 1999]
- **Goals of care** for patients & families
- Preparation for dying
- AND v DNR; place & model of care for dying: **"allow natural dying" order**
- Active symptom management
- Accompaniment & bereavement care

Staff Burnout - Demoralization

- Loss of commitment, role dissatisfaction, negative attitudes to patients/staff/self
- Prevalence: 27% UK oncologists (Ramirez 1995) GHQ caseness; 11-25% nurses (Vachon 2000); **42% MSK surgeons burnout & 27% psych caseness (Guest et al, 2011).**
- Oncology / ICU / mental health > palliative care
- Depression, substance abuse, PTSD, adjustment disorder

Communication Skills

- Promote person-centered care by whole multidisciplinary treatment team
- Information recall 25% (Dunn 1993)
- Poor information provision increases depression (Fallowfield 1990)
- Communication skills sustains behavior change with adequate dose (20 v 40 hrs) (Rasavi 2000, 2003)

Memorial Sloan-Kettering Cancer Center

comskil LABORATORY

CURRICULUM

Modules
1. Breaking bad news
2. Discussing prognosis
3. Shared Decision-making
4. Difficult patients – anger
5. Unexpected adverse surgical events
6. Running family meetings
7. Using an interpreter
8. Transitioning to palliative care
9. Talking about death & dying
10. Clinical trial enrolment

EXPERIENCE

- **Over 1000 faculty & fellows trained**
- **High satisfaction**
- **Global empathy ↑ 37% (Bylund 2009)**
- **Growth in confidence for 92% (Brown 2010)**
- **R25 to now study patient outcomes**

(NCI grant - R25CA134252)

Behavior change from CST at MSKCC

Pre-post CST video coding of Outpatient clinic visits

(N= 120 physicians)

Skill uptake: effect size, Cohen's D
- **Agenda setting: 0.80**
- **use of a framework: 0.63**
- **Check understanding: 0.55**
- **Empathy: 0.44**

Use of appropriate strategies
- **From 42% to 58% (p<.05)**

Use of appropriate process tasks
- **From 65% to 80% (p<.01)**

Comskil coding schema

Facilitation model in training
- **Standardized model of CST**
- 55 facilitators significantly grew in confidence facilitating role-play (*p*<.001).
- Fidelity of Facilitation: inter-rater reliability kappa = 0.82, effect sizes were 0.59 to 0.81 for skill growth.

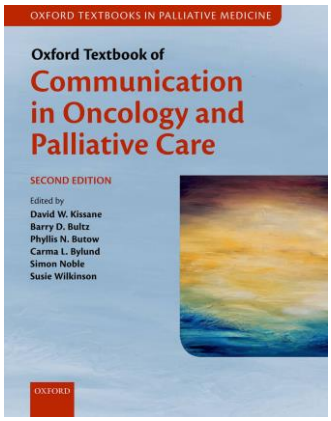
Facilitator Assessment Coding System (FACS)

Communication

- Patients' understanding, recall & satisfaction increases with:
  - **audio-taping** consultations/**summary letter** / ['copy of file' in future]
  - CD-based, booklet, web-based information
  - **Presence of support person**
  - Decision aids that encourage questions: **question prompt sheets**

Go to 2nd Edition, 2017

Oxford University Press 2010



Second Edition 2017

Brought into OUP Textbook series

65 chapters

E-Book

www.oxfordmedicine.com

Canadian artist: Robert Pope

Countering relational dysfunction

- Group therapy for the isolated
- Family therapy whenever communication, cohesion or conflict present problems to family functionality.
- Routine family meetings are crucial during all inpatient palliative care admissions

8. Bereavement care

What about caring for families?

(Continuity of care)

Family-centered care

- Preventive for families 'at risk': starts in oncology when advanced cancer status clear
- Screening can recognize dysfunction
- Key role for psychosocial care team

[Kissane et al, AmJPsychiat, 2006]

Screening with 12-item FRI

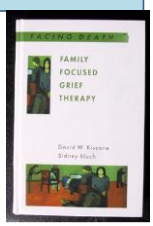
[Family Relationships Index, Moos & Moos, 1974]

Study of 1809 US cancer patients (Schuler et al. 2014)

Family type	Number	%
Well functioning families = approx two thirds		
Supportive families	814	45
Conflict-resolving families	418	23
Families at some risk of poorer outcome = one third		
Low communicators	375	21
Uninvolved families	101	5.5
Conflictual families	101	5.5

Proof of concept: Family-focused care to 'at risk' families in palliative care & bereavement

Kissane et al, 1998, 2002, 2006

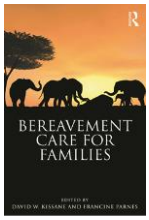


- **Melbourne RCT for 81 families, 333 individuals**
- **Initial efficacy study**
- **Participation rate 44%**

- Main effect: significantly reduced BSI-Distress in FFGT arm at 13 months bereavement
- Outcomes: significant reduction in BDI Depression and improved Social Adjustment
- 16 therapists; 5 sites – 2 hospitals & 3 home care Services

Effectiveness RCT: Family-focused care to 'at risk' families in palliative care & bereavement

- New York RCT for 170 families, 620 individuals
- Screened 4188, ineligible 2700 (65%), eligible 1488 & enrolled 620 (42%)
- 32 therapists, 5 sites – 2 hospitals & 3 home care services
- **Dose UC v 6 v 10 sessions FFGT**
- **Stratified by 3 levels dysfunction:**
  - **low communicators (intermediate)**
  - **less involved (sullen)**
  - **conflictual families (hostile)**



Impact of FFGT on "Prolonged Grief Disorder" caseness – ICD-11

CGI[a] Caseness	Time	Standard Care % (n/total)	FFGT 6-session % (n/total)	FFGT 10-session % (n/total)	GEE effects[b]
	Baseline	CGI data not collected pre-death			Treatment main effect Wald Chisq = 8.31, df = 2, p = 0.016
	6 months bereavement	19.3 (11/57)	12.3 (13/106)	8.9 (9/101)	
	13 months bereavement	15.5 (13/84)	12.1 (15/124)	3.3 (4/122)	

[a]CGI caseness applied criteria for Prolonged Grief Disorder. [b]Test statistics were based on a GEE model of CGI caseness as a function of 5 covariates: study stratification factors (site and family type), treatment assignment, time (e.g., 6 months vs. 12 mos), and a fifth covariate of a treatment by time interaction. The Wald Chi-square statistics were from the Wald test for the treatment by time interaction.

Why might FFGT impact more on PGD and not MDD?

Prolonged Grief Disorder

- Disorder of attachment
- Family relational processes impacted

Major Depressive Disorder

- More biological disorder of neurotransmitter abnormalities and pruning of neuronal dendrites in limbic circuits
- Has secondary effects on relationships

Conclusion

Psychosocial oncology
is
a basic human right

THANK YOU