Cancer Care Ontario

The CCO Management of Depression in Patients with Cancer Guideline: Clinical realities and opportunities for interventional research

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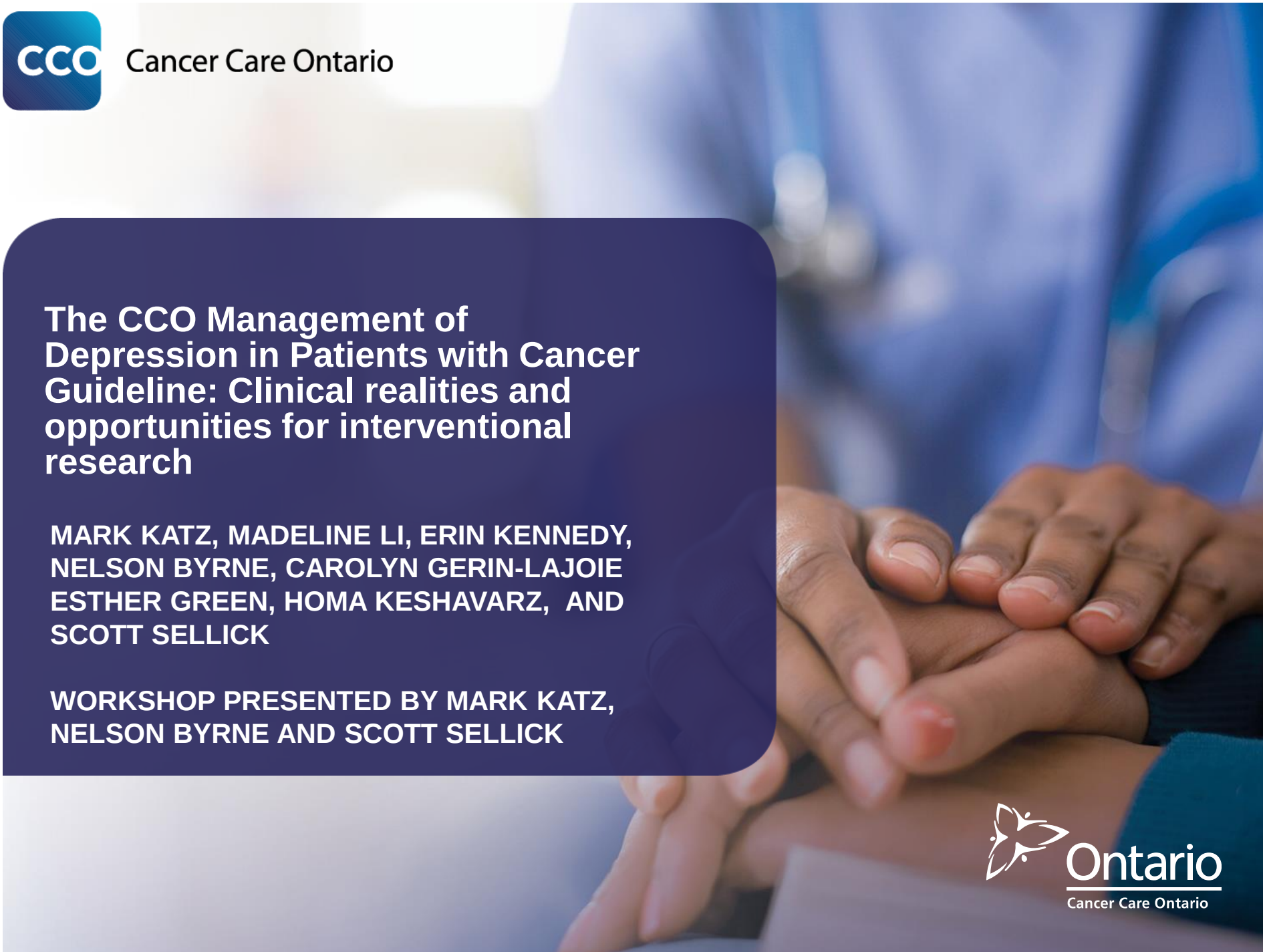

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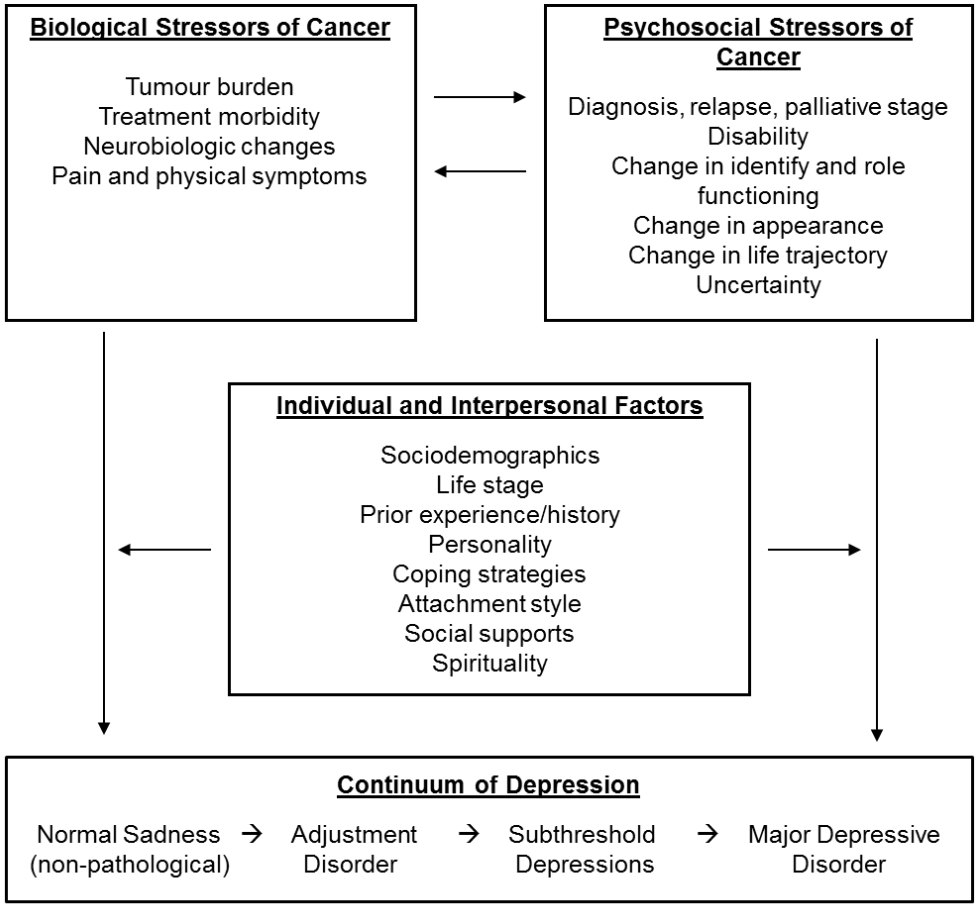
Depression as a Final Common Pathway of Distress Bio-Psycho-Social Etiology



Requires individual bio-psycho-social approach to treatment

The Continuum of Depression

Normal Sadness →	Adjustment Disorder ⇒	Subthreshold Depression →	Major Depression
• Maintains intimacy and connection • Belief that things will get better • Can enjoy happy memories • Sense of self-worth fluctuates with thoughts of cancer • Looks forward to the future • Retains capacity for pleasure • Maintains will to live	• Marked distress or functional impairment but not meeting other criteria for major depression • Not specifically defined • Distinction from subthreshold depression may be arbitrary • Often transient and self-limited	• Similar low mood presentation as major depression but not meeting full criteria for symptom number or duration • Includes persistent depressive disorder if > 2 years duration • Includes episodes lasting < 2 weeks	• Feels isolated • Feeling of permanence • Excessive guilt and regret • Self-critical ruminations/loathing • Constant, pervasive and non-reactive sadness • Sense of hopelessness • Loss of interest in activities • Suicidal thoughts/behaviour

Challenges in the Diagnosis of Depression

- Clinical depression vs. the normal dysphoric response
- Overlap between physical symptoms of disease vs. depression
- Normalizing or rationalizing the depression
- Patient discomfort in expressing emotional pain
- Caregiver discomfort or time constraints in exploring emotional issues
- As a result of these issues depression in cancer tends to be underdiagnosed and undertreated

Prevalence of Depression in Cancer

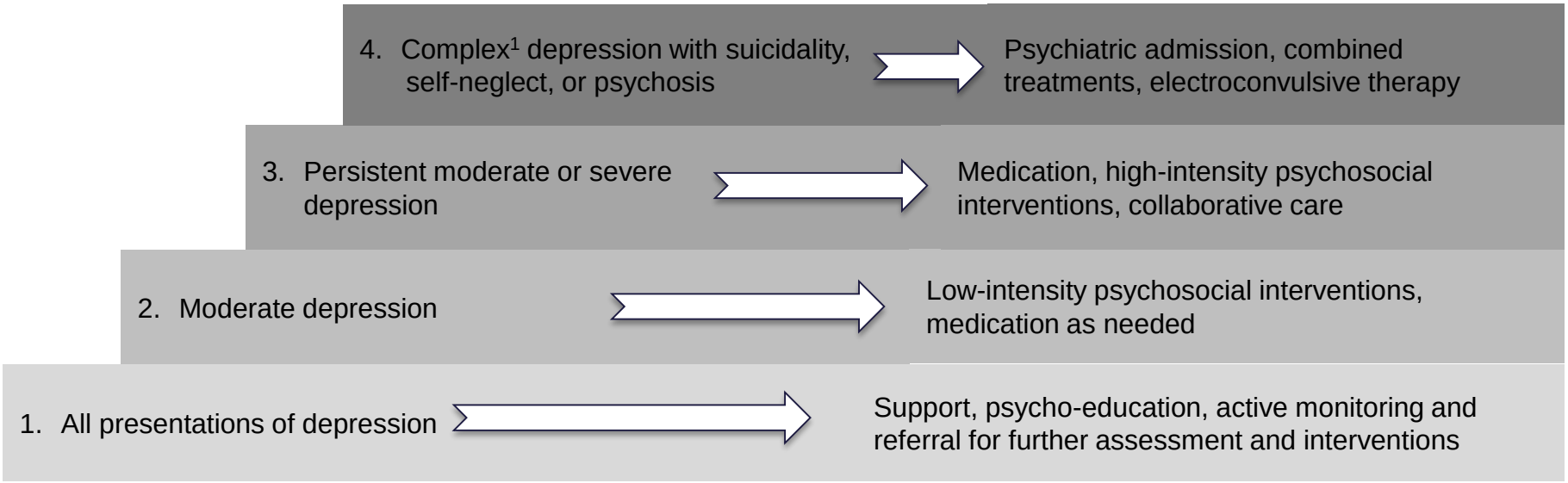
- Major Depressive Disorder: 5-10%
- Other Depressive Disorders: 10-20% (Adjustment Disorder with Depressed Mood, Minor Depression, Chronic Dysthymia)
- 25% "clinically significant depression"
- (Hotopf et al,2002; Raison and Miller,2003; Rodin, Nolan and Katz,2005))

Consequences of Untreated Depression in Cancer

- Worsened quality of life
- Reduced coping with physical symptoms (e.g.pain)
- Increased health care utilization
- Non-compliance with treatment
- Increased likelihood of suicide
- A predictor of early death in some studies with cancer patients

(Massie and Popkin, 1998; Pirl and Roth, 1999; Lloyd-williams et al, 2009))

The Stepped Care Model of Depression Care



General Management Principles

1. Provide psychoeducation about the nature of depression
   - Consider patient handouts such as those in: MacArthur Toolkit (goo.gl/F4Q6Em), Mood Disorders Canada (goo.gl/m6YTNG), APA (goo.gl/QUD9CQ)

2. Inform about the impact of depression on cancer outcomes
   - Reduced quality of life, intensification of physical symptoms, longer hospital stays, reduced survival (Currier 2014)

3. Many do not have psychiatric history, may require destigmatizing of depression
   - Depression may be understandable but can be disabling in its own right; the symptom management approach

General Management Principles

4. Assess and optimize cancer-related physical symptom control and investigate medical contributors to depression eg hypothyroidism, iron deficiency anemia
5. Consider use of a validated depression rating scale to monitor change over time
   - e.g. PHQ-9, HADS, BDI-II (Mitchell 2012)
6. Discuss treatment options attending to patients' preferences and previous treatment experiences
7. Encourage family support and involvement, education and communication

The CCO Management of Depression in Patients with Cancer Guideline

M Li, E Kennedy, N Byrne, C Gerin-Lajoie , E Green, M Katz, H Keshavarz, S Sellick and the Management of Depression in Cancer Patients Expert Panel

- A quality initiative carried out with PEBC
- Released May 2015
- Update on the field since previous guideline released 2007 which identified only 7 low quality psychopharmacologic trials and 4 psychotherapeutic trials
- Clinical Practice Guideline accepted for publication in Journal of Oncology Practice
- Systematic Review and Meta-analysis submitted to Psycho-Oncology

Guideline Methodology

- Population of interest subjects diagnosed w MDD or having suspected depressive disorder based on scoring above threshold for depression on validated instrument
- Examined other guidelines, systematic reviews and RCT
- Three areas of focus: pharmacotherapy, psychotherapy and the emerging field of collaborative care interventions for depression in cancer
- Eligible studies identified: only 2 psychopharmacologic and seven psychological therapy RCT published in the last 10 years; 8 collaborative care trials identified
- Guidelines developed from results of systematic review and meta-analysis, supplemented by previous CPG (NICE, EPCRC) and expert consensus within working group
- Draft guidelines went through process of internal and external review

Psychopharmacologic Treatment of Depression in Cancer

- Limited literature provides modest support for antidepressants
- a handful of RCT, some of poor quality and using low doses and small numbers of subjects, have evaluated older SSRI, TCA and mianserin; most but not all support usefulness of antidepressants
- Case series, open-label studies, and head to head studies without control groups suggest that venlafaxine, citalopram, escitalopram ,sertraline, mirtazapine and bupropion are useful
- (Rodin, Lloyd, Katz et al, 2007; Li Fitzgerald and Rodin, 2012; Hart et al 2012; Laoutidis and Mathiak, 2013)

Limitations in the Literature

- Many more systematic reviews and meta-analyses than actual RCT have been published
- More RCT of antidepressants for hot flashes in breast cancer than for treatment of depression in cancer
- No guidance on treatment resistant patients
- No studies using combination strategies for example combining antidepressants with long-acting psychostimulants, atypical antipsychotics or other antidepressants (eg bupropion XL or mirtazapine)
- There is a limited literature looking at short-acting psychostimulants and atypical antipsychotics in palliative care
- In general we approach the cancer patient with MDD as we would patients without cancer

Psychopharmacologic Trials for Depression in Cancer: CCO Guideline

- Trials since 2005 only a 2006 placebo controlled trial of paroxetine vs desipramine and a 2014 study of methylphenidate vs. placebo augmentation of mirtazapine
- Meta-analysis performed on 5 studies including previously identified from earlier review that included placebo comparisons with fluoxetine and mianserin (not available in North America)
- Key findings: pharmacotherapy more effective than placebo; all studies were short-term

Meta-analysis of pharmacologic interventions

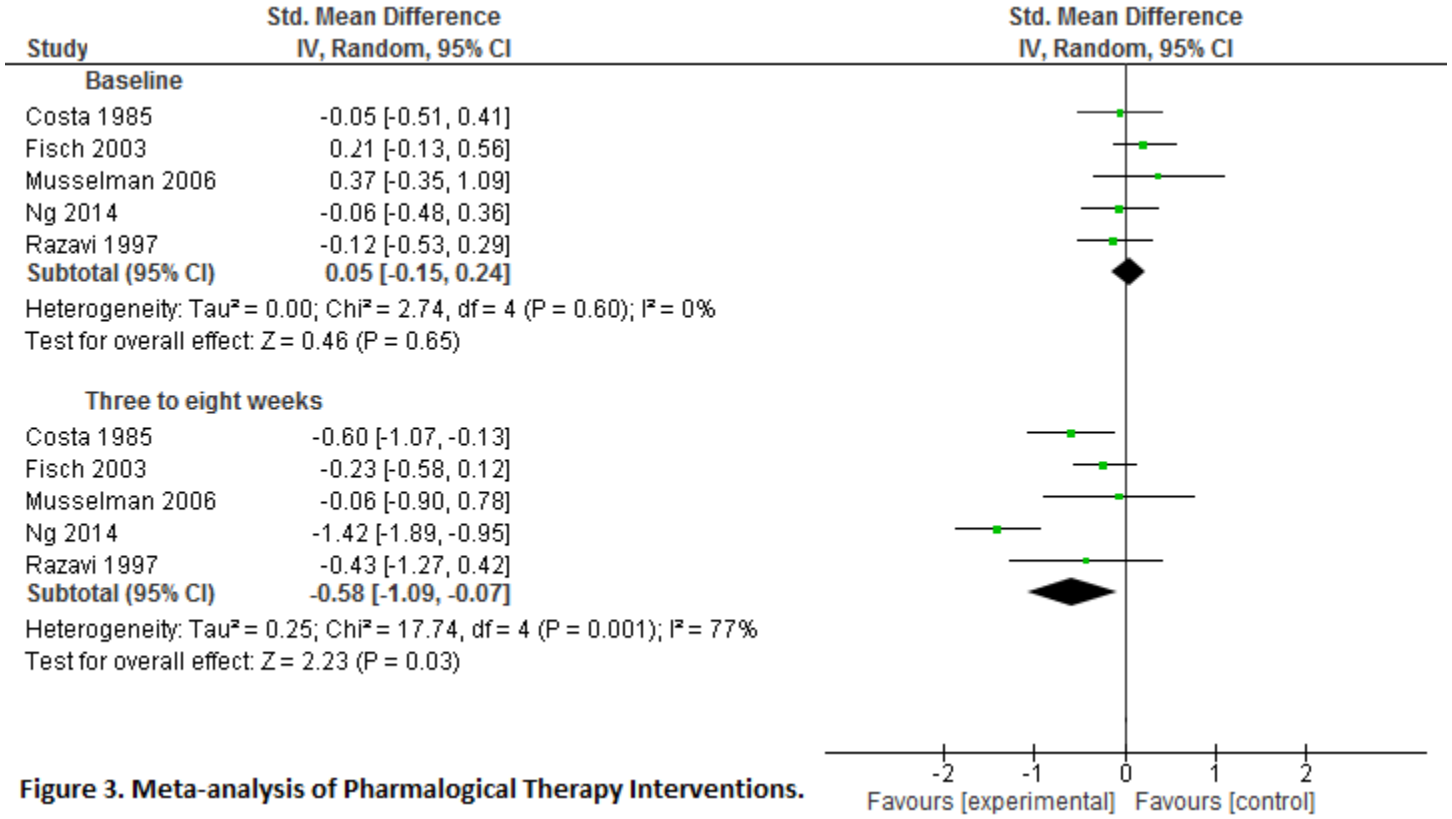


Figure 3. Meta-analysis of Pharmalogical Therapy Interventions.

Recommendations from Guideline about pharmacologic treatments for depression

- Based on limited evidence base, previous CPG, and expert panel consensus
- Effectiveness of psychosocial and pharmacologic treatments for moderate depression is equal
- Pharmacologic interventions are more effective for severe depression
- Combined interventions should be considered for severe depression
- Antidepressants should be reserved for moderate to severe depression, can be used in persistent milder cases or if depression interfering with cancer treatment engagement

Recommendations from Guideline about pharmacologic treatments for depression

- No antidepressant can be recommended as more effective than any other; choice depends on factors like
- past psychiatric history of response,
- family history of response,
- potential for drug interactions,
- somatic symptom profile;
- potential for dual benefit eg for pain or hot flashes;
- type of cancer (avoid bupropion in CNS cancers),
- comorbidities (avoid psychostimulants or TCA in cardiac disease)
- prognosis (psychostimulants with shortened life expectancy as onset quick)

Barriers to psychopharmacologic trials for depression in cancer

- **Difficulties with recruitment** due to competing clinical trials; reluctance to refer or enroll patients for placebo-controlled trials when widespread use of newer antidepressants already in practice; concern about efficacy or safety from referring oncologists

- **Difficulties obtaining funding** because most drug trials are pharma sponsored; depression pharma companies fearful of adverse events in cancer patients
- (Park et al 2014)

Clinical realities in the pharmacologic treatment of depression in cancer: prevalence and type of antidepressant

- Antidepressant use in cancer patients for depression is widespread (estimates range from 14-18% of cancer patients on an antidepressant for depression/anxiety, especially in North America; lower rates in Europe and especially Asia
- Prevalence of antidepressants range from 14.8% to 27.1% for uses other than pain in advanced cancer; prevalence of antipsychotic use 40% (Farriols et al, 2012; Janberidze et al 2014)
- Most commonly used antidepressants are SSRI like citalopram/escitalopram, mirtazapine and duloxetine (Farriols et al, 2012)

Selecting a first-line antidepressant in cancer patients

- Choose one you are comfortable with, with limited potential for side effects and drug interactions
- SSRI: escitalopram
- SNRI: desvenlafaxine or venlafaxine; duloxetine w comorbid pain
- Mirtazapine: comorbid anorexia, weight loss, insomnia, anxiety
- Bupropion XL: comorbid anergia, sexual dysfunction, cognitive complaints
- Vortioxetine: depression with cognitive complaints
- Psychostimulants in advanced cancer/palliative context

What to do when the patient is not improving?

- No published evidence in cancer to guide us
- Recommendations come from clinical expertise and extrapolation from general psychiatric literature
- Optimize dose; augment or combine with another agent; switch to another class

Augmentation: Clinical context may be important

- The patient with residual fatigue, cognitive complaints, chemo brain on an SSRI or SNRI: consider psychostimulant eg methylphenidate or lis-dexamfetamine, aripiprazole (atypical antipsychotic) or bupropion XL
- The patient with residual anxiety, insomnia, anorexia, extreme hypervigilance about recurrence: consider quetiapine XR, aripiprazole, lurasidone or mirtazapine rather than benzodiazepine

Psychotherapeutic Strategies in Cancer

- Cognitive Behavioral (CBT)
- Behavioral Activation (BAT)
- Interpersonal (IPT)
- Problem Solving Therapy (PST)
- Supportive Expressive (eg CALM therapy –PMH)
- Meaning Centered or Existential
- Dignity Therapy

Cognitive Behavioral Therapy for Depressed Cancer Patients

- CBT addresses negative thoughts about the self, world or future that are prominent in depression
- Involves keeping thought records, recording connections between situations, moods and thoughts and teaches one how to critically evaluate one's thoughts
- Key intervention is 'cognitive restructuring' the reframing of negative thoughts through an analysis of the evidence for and against negative thoughts, and the correction of cognitive distortions
- Recent interest in combining with mindfulness practice and delivering in group format (mindfulness based cognitive therapy)
- Can be quite useful where patients misinterpret bodily sensations and overestimate likelihood of recurrence

Behavioral Activation for Depressed Cancer Patients

- Focuses primarily on examining the consequences of depressed behaviors (reduce opportunities for positive reinforcement) and developing a gradual plan for becoming more mobilized and active
- Activity scheduling emphasizing mastery and pleasure experiences
- Avoiding avoidance behaviors
- Recent evidence for equivalent effectiveness to problem solving therapy in depressed cancer outpatients (Hopko et al, 2009, 2011)

Supportive-Expressive Therapy (also known as psychodynamic)

- Therapeutic relationship
  - Reflective space
  - Empathic understanding and validation
  - Affect regulation
- Mentalization
  - I.e. distinguish facts from feelings
- Joint creation of meaning and new narratives
- Attention to the whole person

Problem Solving Therapy

- Focuses on effective coping with stressors by teaching problem solving skills
- Fosters adaptive attitudes and behaviours
- 8 treatment sessions delivered in person or by phone, individual or with support person
- Can be delivered by non mental health professionals eg trained nurses
- Most common therapy employed in collaborative care interventions
- Components involve : skills to enhance multitasking (externalization, visualization, simplification), skills to reduce emotional arousal that affects problem solving; problem solving tasks eg defining problem and goal setting; brainstorming, decision making, developing action plan, implementation and evaluation (Nezu et al, 2013)

Areas of Promise in Psychotherapy for Advanced Cancer

- 3 newer therapies targeting advanced cancer populations
- Not yet reported in depressed subgroups
- Dignity therapy (Chochinov et al, 2011)
- An individual, legacy project intervention for palliative patients using a tape recorded interview based on a 9 question interview protocol. The dignity interview focuses on issues that matter most or that the patient would most want remembered. Edited transcripts of the interview are given to patients to share with family.
- Meaning Centred Psychotherapy (Breitbart et al, 2012)
- A brief intervention focusing on historical, attitudinal, creative and experiential sources of meaning developed for advanced cancer patients. Developed as either an 8 wk group or 7 wk individual intervention.

Areas of Promise in Psychotherapy for Advanced Cancer

- CALM (Lo et al, 2014)
- A brief, manualized, semi-structured individual and couple-based psychotherapy designed to alleviate distress in patients with advanced cancer.
- 3-8 sessions delivered over 6 months that addresses four broad domains: symptom management and communication with health care providers, changes in self and relations with close others, sense of meaning and purpose, and the future and mortality
- supportive-expressive individual therapy shown to alleviate depressive distress and death anxiety and to improve the sense of meaning and peace (spiritual well-being).

Psychotherapeutic Trials for the Treatment of Depression in Cancer: The CCO Guideline

- Nine eligible RCT identified; seven since 2005
- CBT, PST, BAT, supportive therapy, “narrative therapy”, and psychodynamic psychotherapy were studied
- 6 studies involved no treatment or usual care group and were included in the meta-analysis
- 4/6 studies had evidence favouring CBT, PST, supportive therapy and dynamic over control conditions
- One study comparing BAT to PST no difference
- Meta-analysis demonstrated significant post-treatment differences that did not persist at longer term follow up assessments in the 4 studies that looked at longer term outcome

Meta-analysis of psychological treatments

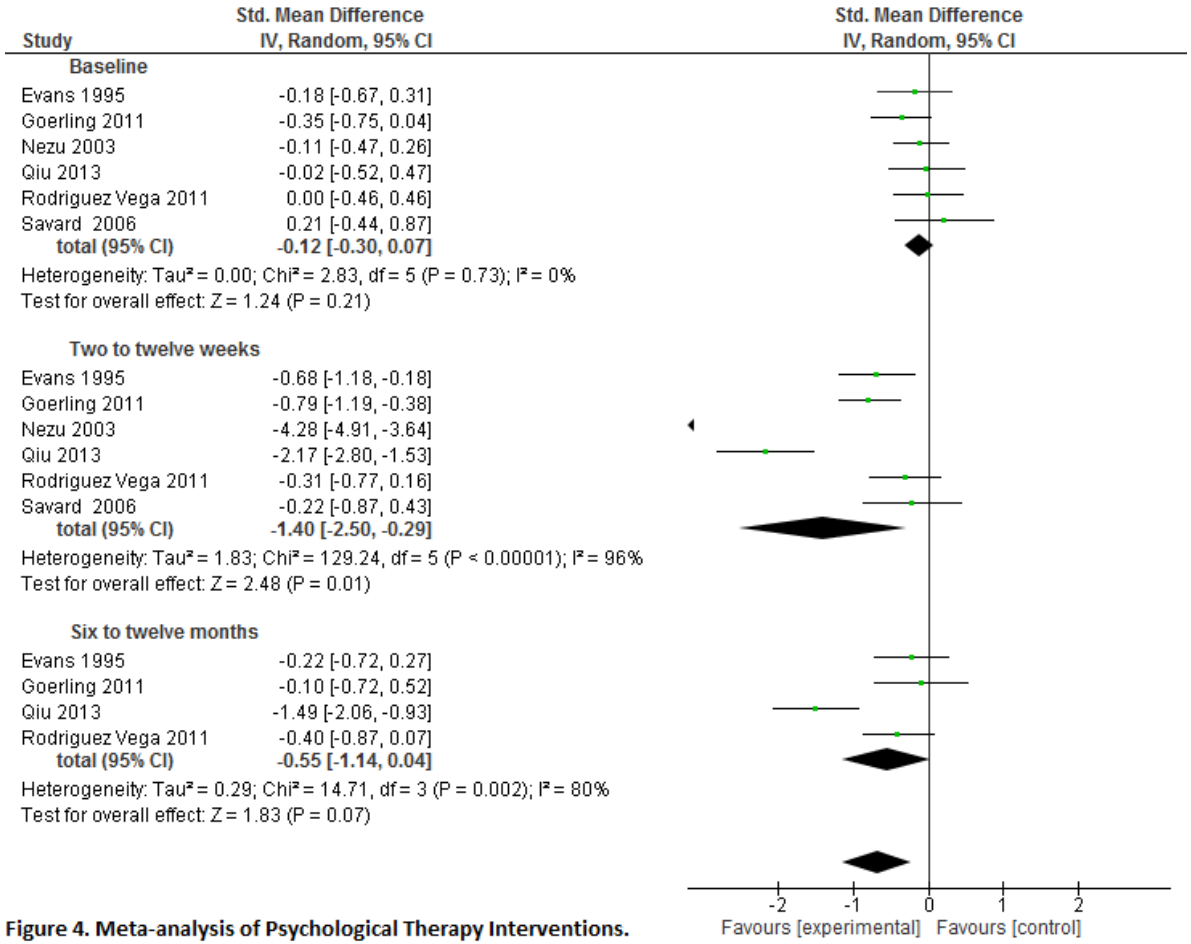


Figure 4. Meta-analysis of Psychological Therapy Interventions.

Recommendations from Guideline regarding psychotherapy for depression in cancer

- Mild to moderate depression should be treated with psychotherapy alone in most cases (considered first)
- Insufficient evidence exists to support one modality over another; choice should be based on patient factors and local resource availability
- Psychological therapies (CBT,IPT, dynamic psychotherapies)should be delivered by health care professionals competent in the modality; non mental health specialists can be trained in basic psychosocial interventions like empathic communication, psychoeducation, PST or BAT

Clinical issues in delivering psychotherapy to depressed cancer patients

- Patient challenges to engage in psychotherapy due to:
- pain, fatigue, cognitive issues
- ability to attend regular appointments, missed appointments due to illness
- denial/ defensiveness (the tyranny of positive thinking; avoidance or mortality fears)

Clinical issues in delivering psychotherapy to depressed cancer patients

- System factors:
- Availability of trained therapists
- Workload burden of therapists and competing demands eg response to screening, crises vs scheduled appointments
- Mandate from cancer centre/ hospital employers limiting role activities or number of sessions
- Lack of outcome measurements embedded within electronic health record to provide quality data on efficacy
- Lack of supervision and mental health expertise in Psychiatry/Psychology for difficult cases

Components of Collaborative Care for Depression

- Involve active collaboration between a primary care physician or oncologist who prescribes antidepressants and monitors the patient, a care manager (usually an RN) who provides psychoeducation about depression, PST or BAT, and a psychiatrist or psychologist who provides regular supervision to the care manager and guides treatment
- Measurement based care (eg PHQ-9) to monitor progress
- Regular supervision/case conferences
- Flexible treatment plans with range of treatment intensity (psychosocial treatment, antidepressants or both depending on patient situation) based on stepped care model

Potential advantages to the Collaborative Care model for depression in cancer care delivery

- Ensures timely follow up and compliance with treatment; eg enhanced uptake and compliance with antidepressants
- Often involves algorithm-based approach for medication and manualized psychosocial intervention which enhances outcomes
- Useful for mild, moderate and severe cases because of flexibility
- Particularly useful where primary depression care by psychiatrist or psychologist not feasible because of staffing availability issues

Examples of Collaborative Care Interventions for depression in cancer

- The ADAPT-C Trial (Ell et al, 2008 and 2011)
- Low income Hispanic cancer patients were randomized to CC intervention with PST, antidepressant medication or both compared to enhanced UC
- Enhanced UC involved providing psychoed about depression and notifying the patients oncologist about their depression
- 94 received PST; 71 received both; 10 received antidepressants only
- In the EUC condition few patients received any treatment for depression
- Response rates were 63% compared to 50% at 12 months favoring CC group; 46% to 32% at 24 months

Collaborative Care Interventions for the treatment of depression in cancer: the CCO Guidelines

- The SMART-Oncology Trials (Strong et al 2008; Sharpe et al 2014; Walker et al, 2014)
- CC for patients with cancer and MDD involving PST over 10 sessions, psychoeducation and guidance support/around trying an antidepressant vs. usual care
- Improved response and remission of depression in the collaborative care group with persistence of benefits at 12 months
- Again usual care group tended to receive no treatment

Meta-analysis of collaborative care interventions

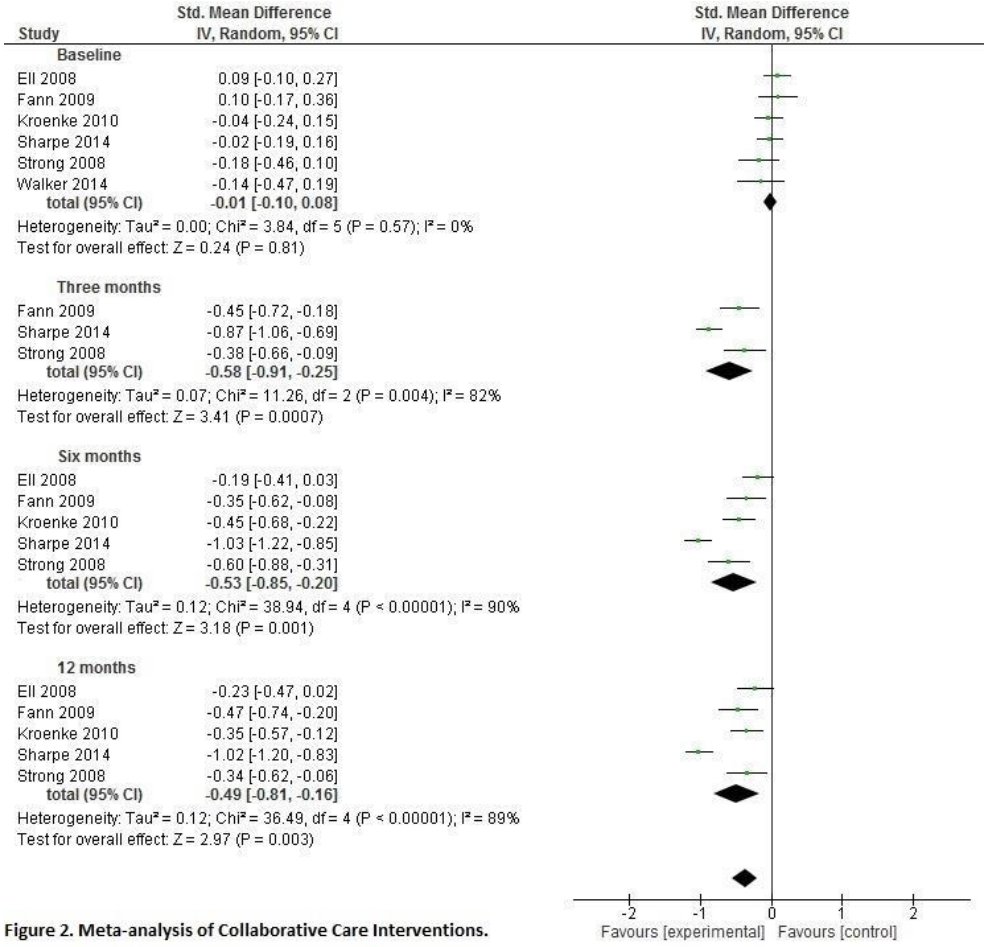


Figure 2. Meta-analysis of Collaborative Care Interventions.

Recommendations from the Guidelines regarding Collaborative Care

- The collaborative care studies were noted to be better designed, more robustly powered, and of higher quality than the psychopharmacologic and psychological treatment studies reviewed
- Benefits of these intervention were more robust and sustained over time
- Collaborative care interventions should be considered for cancer patients diagnosed with Major Depression.
- This may imply a significant restructuring of care delivery, which may be a challenge for institutions
- A renewed research agenda to strengthen the evidence base around the specific components of collaborative care is urgently needed to justify the investment of resources for this reorganization

Clinical and systemic issues in delivering a collaborative care model for depression in cancer

- Studies have tended to look at populations where usual care tended to mean no treatment; how would collaborative care interventions fare against models that provided excellent usual care?
- What are the costs of delivering CC interventions, eg the hiring of a nurse care manager vs the benefits (economic analysis)
- Palliative care delivery relies heavily on NP, advanced practice nurses- already use a collaborative care model

Some areas for future research

- 1) Newer antidepressants vs placebo (have we moved beyond this?)
- 2) Newer antidepressants head to head (plus placebo)
- 3) Targeted subgroups: eg vortioxetine or bupropion XL for depression and brain fog; mirtazapine vs. placebo in advanced cancer
- 4)studies in treatment resistant patients including augmentation trials
- 5) comparison trials of psychotherapy (CBT vs. supportive expressive)
- 6) studies of newer therapies (CALM, dignity, meaning centred) in depressed subgroups
- 7) collaborative care: comparison with other modalities including economic analysis; study of cc components