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Pharmacotherapy: Risks and Benefits

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Disclosure Statement 2007-2008

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Speaker/Advisory Boards
- AstraZeneca
- Biovail
- CANMAT
- Eli Lilly
- GlaxoSmithKline
- Janssen
- Litebook Company, Inc.
- Lundbeck
- Servier
- Wyeth

Stockholder
- None

Clinical Trials/Grants
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- CANMAT
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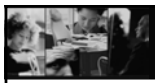
- Litebook Company, Inc.
- Mathematics of Information and Advanced Technology Systems
- VGH-UBC Hospital Foundation

Outline

- Antidepressant efficacy, effectiveness and tolerability
- Antidepressant safety
  - Suicidality
  - Drug interactions
- Measurement-based care
- Maintenance treatment
- Managing limited or partial response
  - Sequencing
  - Combination treatment

Profile of the ideal antidepressant

- Safe
- Well tolerated
- No drug interactions
- Simple to use
- Rapid onset of action
- Excellent efficacy to remission
- Broad spectrum (depression & anxiety)
- Good relapse/recurrence prevention
- Inexpensive



Antidepressants - c 2008

TCA
Amitriptyline
Imipramine
Clomipramine
Trimipramine
Maprotiline
Amoxapine
Nortriptyline
Desipramine

MAOI
Phenelzine
Tranylcypromine

SSRI
Citalopram [Celexa]
Escitalopram [Cipralex/Lexapro]
Fluoxetine [Prozac]
Fluvoxamine [Luvox]
Sertraline [Zoloft]
Paroxetine [Paxil]

SARI
Trazodone
{Nefazodone}

NDRI
Bupropion-SR/XL [Wellbutrin]

SNRI
Duloxetine [Cymbalta]
Venlafaxine-XR [Effexor]

NaSSA
Mirtazapine [Remeron]

RIMA/B
Moclobemide [Manerix]
Selegiline patch [EMSAM]

CANMAT

CANMAT Depression Guidelines Revision, 2009

- Evidence-based update of 2001 CPA/CANMAT Guidelines
- Psychotherapy, pharmacotherapy, complimentary therapies, neurostimulation treatments
- Question-Answer format
- International commentary
- Published as a supplement in the Journal of Affective Disorders

www.canmat.org

"There's been a lot of research lately on your condition. Now I'm sorry I didn't read any of it."

CANMAT Depression Guidelines Revision, 2009

Evidence for antidepressant efficacy and effectiveness, since 2000:

- 224 randomized controlled trials.
- 30 systematic reviews and meta-analyses.
- 3 major reports.
  - Agency for Healthcare Research and Quality (US). Comparative effectiveness of second-generation antidepressants, 2007.
  - Collegium Internationale Neuro-psychopharmacologicum (Intl). The use and usefulness of antidepressants: A technical review of evidence, 2006.
  - National Institute for Clinical Excellence (UK). Management of depression in primary and secondary care, 2004

First-line Antidepressant Tolerability

Product	Sedation	Insomnia	Headache	GI Distress	Asthenia / fatigue	Weight Gain	Sexual Issues	Dizziness	Tremor	Constipation	Sweating	Dry Mouth
Bupropion XL	○	●	○	●	○	○	○	○	○	●	○	●
Duloxetine	○	●	○	●	○	○	○	○	○	●	○	●
Escitalopram	○	○	○	●	○	○	○	○	○	○	○	○
Mirtazapine	◕	○	○	○	●	◕	○	○	○	●	○	●
Paroxetine	●	●	●	●	●	○	◕	●	●	●	●	●
Sertraline	●	●	●	◕	○	○	◕	●	●	○	○	●
Venlafaxine XR	●	●	●	◕	○	○	◕	●	○	○	●	●

○ <2% ◔ 2–5% ◑ >10% ◕ >30%

Adapted from: Kennedy SH, et al. Can J Psychiatry 2001;47(Suppl 1):38S-58S with updates from the e-CPS.

Antidepressant Medications: General Conclusions

- Antidepressants demonstrate clear efficacy versus placebo, although effect sizes are mild to moderate
  - Placebo rates are high (and increasing)
  - Greater efficacy when clinical outcomes are measured
  - More evidence for efficacy when severity is moderate to severe
- SSRIs and third-generation agents are as effective but better tolerated and safer than older medications
- Not all antidepressants are alike, even within the same class
- There are no clear predictive factors for choice of agent

Profile of the ideal antidepressant

- Safe
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Suicidality associated with antidepressants in children and adolescents?

- 2003 – of 15 MDD studies done in children/ adolescents, only 6 were published.
- In 3 studies of paroxetine, an excess risk of suicidal behaviours was detected (3.4% vs. 1.2% for placebo).
- 2004 – FDA commissioned a re-analysis of all paediatric clinical trials using Columbia University suicide research group criteria.
- June 2004 – black box warning for antidepressants in Canada and later in US; warning letter and contraindication in UK.

Lam RW, Kennedy SH, 2005

Possible reasons for suicidality associated with antidepressants

- Worsening of underlying depression before benefit of medication.
- Unexpected psychosocial stressor (e.g., relationship breakup).
- Improvement of physical symptoms (e.g., energy) before mood symptoms.
- Non-specific side effect of medication (e.g., headaches, anxiety).
- Specific side effect of medication (e.g., activation syndrome).

Lam RW, Kennedy SH, 2005

Suicidality and antidepressants Summary of evidence

Type of Study	Adults	Youth
RCTs and meta-analyses	**Safe ✓**	**Caution indicated**
Prescription databases	**Safe ✓**	**Caution indicated**
Forensic databases	**Safe ✓**	**Safe ✓**
Pharmaco-epidemiology	**Safe ✓**	**Safe ✓**

Clinical Recommendations ALL AGES

- Patients treated for MDD must be monitored closely for worsening, especially at the start of treatment.
- When medications are used, patients should be educated about side effects including anxiety, agitation, hypomania or suicidality.

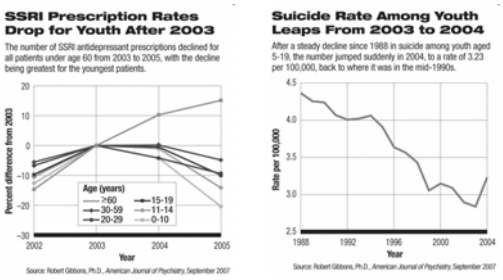
Lam RW, Kennedy SH, 2005

Clinical Recommendations CHILDREN & ADOLESCENTS

- Only fluoxetine has an acceptable benefit-risk ratio to recommend as first-line treatment of MDD.
- Other SSRIs are considered second-line treatments, to be used for MDD that is severe, chronic, comorbid with other conditions, or not responding to psychosocial treatments.
- Paroxetine and other novel antidepressants (e.g., SNRIs) are considered third-line treatments because of higher adverse events profile.
- Tricyclic antidepressants are not recommended.

Lam RW, Kennedy SH, 2005

Negative Effects of the Black Box Warnings?



Psychiatr News, Oct 2007; 42: 1 - 34.

Safety profile of first-line antidepressants

Antidepressant	Safety	Drug Interactions
Citalopram	■	■
Escitalopram	■	■
Fluoxetine	■	**Marked inhibition of CYP 2D6**
Paroxetine	■	**Marked inhibition of CYP 2D6**
Sertraline	■	■
Bupropion-SR/XL	**Caution in overdose**	Moderate inhibition of CYP 2D6
Duloxetine	■	**Avoid inhibitors of CYP 1A2**
Mirtazapine	■	■
Venlafaxine-XR	**Caution in overdose**	■

■ No issues

Benefit-Risk Assessment for Antidepressants in Major Depressive Disorder

Group	Medication	Benefit (Efficacy)	Risk (Suicidality, etc)
Adults (18-65 yrs)	**All antidepressants**	**Level 1**	**Level 2**
Elderly (>65 yrs)	**All antidepressants**	**Level 1**	**Level 2**
Children & Adolescents (<18 yrs)	**Fluoxetine**	**Level 1**	**Level 2**
	Other antidepressants	**Level 2**	**Level 2**

■ Safe/Effective □ Probably safe/effective ■ Caution required

Updated from Lam RW, Kennedy SH, 2004

Antidepressants: Proven Efficacy across a Spectrum of Disorders

- Major depressive disorder
- Dysthymic disorder
- Bipolar depression
- Seasonal affective disorder
- Premenstrual depressive disorder
- Panic disorder
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Social anxiety disorder
- Post traumatic stress disorder
- Bulimia nervosa
- Chronic pain
- Fibromyalgia
- Smoking cessation

B.C. Clinical Guidelines for Depression


GUIDELINES & PROTOCOLS
ADVISORY COMMITTEE

Diagnosis and Management of Major Depressive Disorder

Scope

- Practical recommendations with level of evidence
- Pharmacotherapy and psychotherapy
- Acute and maintenance treatment
- Use of monitoring tools
- Focus on self-management
- Flow sheet

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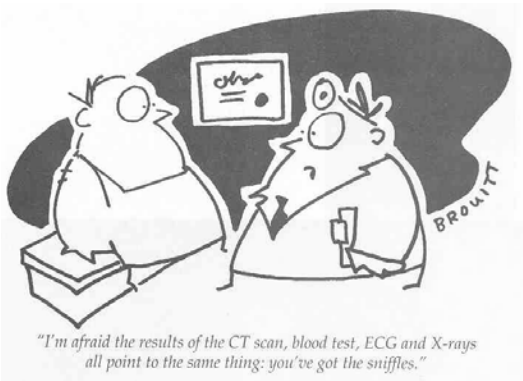


"I'm afraid the results of the CT scan, blood test, ECG and X-rays all point to the same thing: you've got the sniffles."

Using Validated Outcome Measures

CLINICIAN-RATED	PATIENT-RATED
Hamilton Depression Rating Scale (HDRS, Ham-D)	**Beck Depression Inventory (BDI)**
Montgomery Asberg Depression Rating Scale (MADRS)	**Geriatric Depression Scale (GDS)**
Primary Care Evaluation for Mental Disorders (PRIME-MD)	**Personal Health Questionnaire (PHQ-9)**

BC Depression Guidelines: Recommendation #7b – Monitoring Outcomes

The PHQ-9 (Personal Health Questionnaire)


Patient Health Questionnaire (PHQ-9)

- Self-rated scale is the "HbA1c" of depression.
- Takes 3-5 minutes to complete.
- Is highly sensitive and specific for the diagnosis of depression.
- Can be used to monitor progress (including remission criteria scores).

TOTAL SCORE	DEPRESSION SEVERITY
0-4	None
5-9	Mild Depression
10-14	Moderate Depression
15-19	Moderate-severe Depression
20-27	Severe MDD

PHQ-9 is adapted from PRIME MD TODAY, developed by Spitzer RL, Kroenke K, & Williams JBW, ©1999 Pfizer Inc.; Yeung A et al, 2008

There are 2 phases of treatment for depression

Phase	Duration	Goals
Acute	8-12 wks	➢ Remission of symptoms ➢ Return to function
Maintenance	6-24 mos, or longer	➢ Rehabilitation ➢ Prevention of recurrence

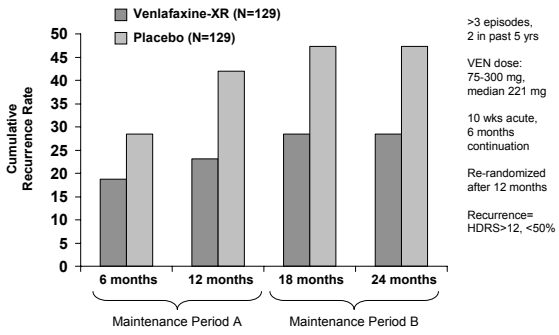
BC Depression Guidelines: Recommendation #1a – Detection

Recommendations for Maintenance Treatment

- ALL patients should continue on antidepressants for 6 months <u>after</u> remission of symptoms
- Patients who require longer maintenance treatment (> 2 years) include those with:
  - Chronic episodes
  - Severe episodes (suicidality, psychosis)
  - Difficult to treat episodes
  - Recurrent, frequent episodes (2 episodes in 2 years, or 3 in 5 years)
  - Older age
  - Comorbidity

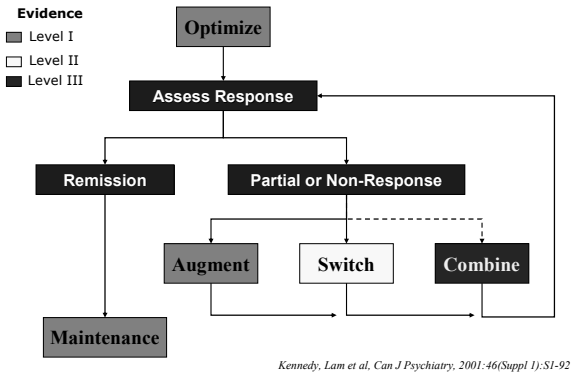
Recommendation #7c – Maintenance Treatment

PREVENT Study for Recurrent Major Depression



Keller MB et al. J Clin Psychiatry 2007; 68:1246-56.

Evidence-Based Algorithm for Non-Response



Kennedy, Lam et al, Can J Psychiatry, 2001:46(Suppl 1):S1-92

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Question:

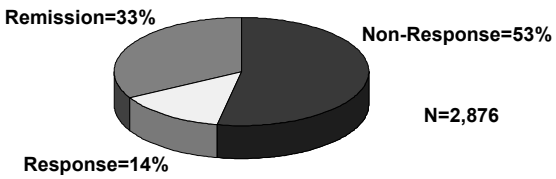
- "What do you do if the first antidepressant doesn't work?"

"State-of-the-Art" Features

- Real-world population
- Large sample size
- "Measurement-based" care
- Focus on remission
- Patient preference/clinical equipoise
- Psychotherapy and pharmacotherapy

Rush AJ et al. Control Clin Trials 2006; 25:119-42.

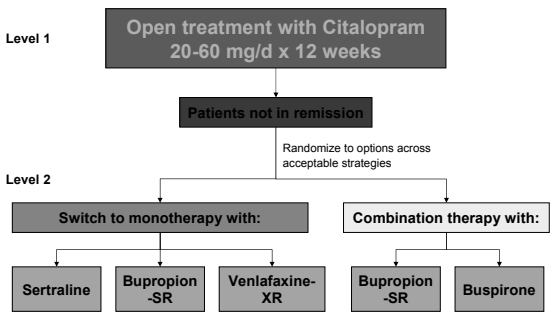
STAR*D Level 1: Response to Citalopram



- STAR*D effectiveness study of moderate to severe depression
- "Real world" patient sample
- Citalopram 20-60 mg/d x 12 weeks (mean dose = 42 mg)
- Outcome by QIDS-SR

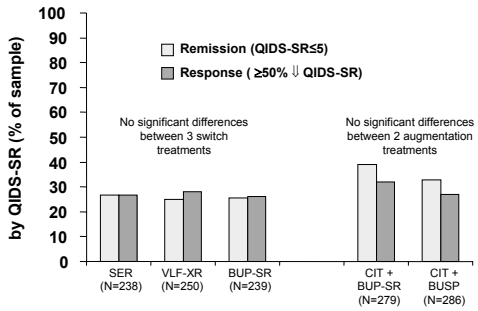
Trivedi MH et al. Am J Psychiatry 2006; 163:28-40

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)



Rush AJ et al. Control Clin Trials 2006; 25:119-42.

STAR*D switch and augmentation strategies



Rush AJ et al. NEJM 2006; 354:1231-42; Trivedi MH et al. NEJM 2006; 354:1243-52.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) – Level 2

Conclusions for 2nd Step

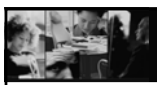
- Switch within class or out-of-class is equivalently effective for SSRI-nonresponders.
- Bupropion combination is more effective and better tolerated than buspirone augmentation.
- May want to use combination before switch in partial responders.

Cumulative Remission Rates in STAR*D

Level	Interventions	Remission Rate*	Cumulative Remission
Step 1 **N=3,671**	• CITALOPRAM	36.8%	36.8%
Step 2 **N=1,439**	• Switch: VEN / BUP / SER • Combine: BUP / BUS • Switch / Combine: CT	30.6%	56.1%
Step 3 **N=390**	• Switch: NOR / MIR • Augment: LI / T3	13.7%	62.1%
Step 4 **N=123**	• Switch: TCP / MIR+VEN	13.0%	67.0%

Rush AJ et al. Am J Psychiatry 2006;163:1905-17.

* QIDS-SR$_{16}$ ≤ 5



Medication strategies for residual symptoms: Add-on to antidepressants

Residual symptoms:	Anxiety, insomnia	Hyper-somnia, fatigue	Concen-tration, memory, ADHD	Cyclicity, bipolarity	Seasonality
Add-on medication strategies	▸ Benzo-diazepine ▸ Atypical anti-psychotic ▸ Mirtaza-pine	▸ Bupropion ▸ Cytomel ▸ Modafinil ▸ Stimulants ▸ Light therapy	▸ Bupropion ▸ Atomox-etine ▸ Modafinil ▸ Stimulants	▸ Quetiapine ▸ Lithium ▸ Lamo-trigine ▸ Atypical anti-psychotic	▸ Light therapy ▸ Bupropion

Note: these recommendations are based only on Level 3-4 evidence currently, but take into account probable efficacy and tolerability.

CANMAT

Antidepressants: Risks and Benefits

- Antidepressants are safe and effective treatments for a spectrum of conditions, but the decision for use must weigh benefits vs. risks for an individual.
- Some people will require more intensive treatment to achieve clinical remission.
- Maintenance treatment is necessary.
- There is no good evidence that suicidality is associated with antidepressants in adults, and only limited evidence for the association in youth.
- ALL patients should be closely monitored for treatment-emergent effects including suicidality.

Antidepressants: What do we need to know?

- What is the comparative effectiveness of agents?
- How effective are medications for real-world outcomes?
- How can we optimize/predict/tailor response?
- When should we combine medications?
- Which medications should we combine?
- How long to maintain on medications or Who can come off medications?
- What are the best medication strategies for comorbid conditions, both psychiatric and medical?

Typical Clinical Trial Depressed Subject

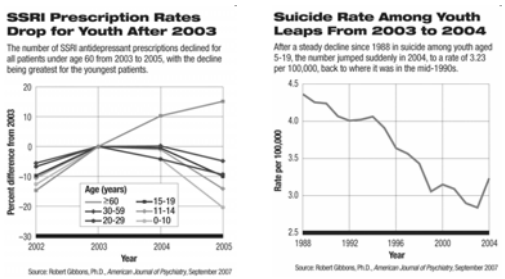
- Single Axis I diagnosis
- Moderately depressed outpatient
- Not actively suicidal
- No medical problems
- No substance abuse/dependence
- No significant personality disorder
- Highly compliant
- Able to spend at least 3 hrs/week in clinic
- Willing to take placebo

Difficulties in Studying Suicidality Associated with Antidepressants

- Suicidality is associated with the underlying disease
- Patients present and start treatment at a time when they are feeling worst
- Suicidality is an uncommon occurrence
- Suicidality can be easily mis-identified
- Other clinical factors may mediate higher risk of suicidality (previous suicidality, comorbid conditions)
- In clinical trials, those at higher risk for suicidality are excluded
- In naturalistic/epidemiologic studies, selection of antidepressants is not random

Lam RW, Kennedy SH, 2005

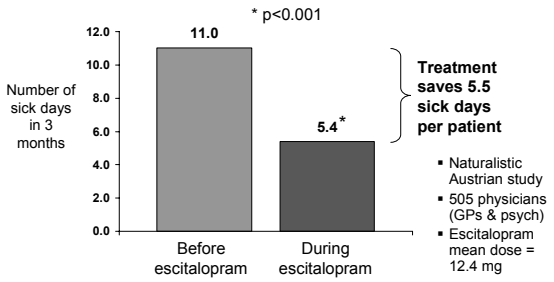
Negative Effects of the Black Box Warnings?



Psychiatr News, Oct 2007; 42: 1 - 34.

Antidepressant Treatment Reduces Sick Days

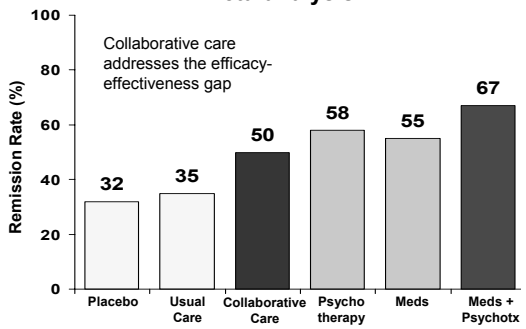
N=2,378 patients treated with escitalopram 10-20 mg/d



- Naturalistic Austrian study
- 505 physicians (GPs & psych)
- Escitalopram mean dose = 12.4 mg

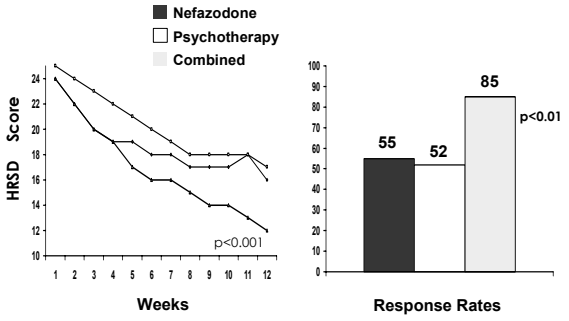
Winkler D et al, Hum Psychopharmacol 2007.

Remission Rates in Primary Care Studies: A Meta-analysis



Dawson M et al, BMC Psychiatry, 2004.

Treatment of chronic depression (n=681)



Keller et al, NEJM, 2000

Back to Main List

Augmentation Strategies c.2004

Proven effective
- **Lithium (TCAs only?)**

Possibly effective
- **Amphetamines**
- **Buspirone**
- **Tryptophan**
- **Omega-3 Fatty Acids**
- **Lamotrigine**
- **Modafinil**

Probably effective
- **T3 (Cytomel)**
- **Atypical antipsychotics**

Not effective
- **Pindolol**

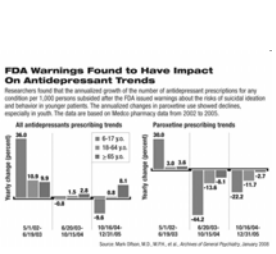
Biological Treatments for Depression, c.2008

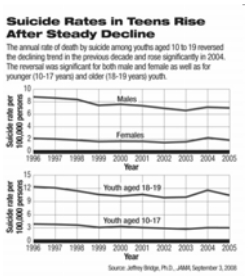
Pharmacologic

- Antidepressants
- Lithium
- Anticonvulsants
- Antipsychotics
- Augmenters

Somatic

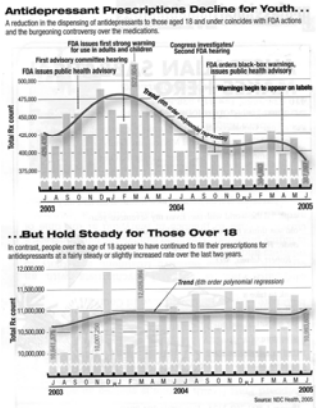
- Electroconvulsive Therapy
- Wake Therapy
- Light Therapy
- Transcranial magnetic stimulation
- Magnetic seizure therapy
- Vagus nerve stimulation
- Deep brain stimulation
- Limbic neurosurgery





Psychiatr News, Feb 2008; 43: 25.

Psychiatr News, Oct 2008; 43: 1 - 23.



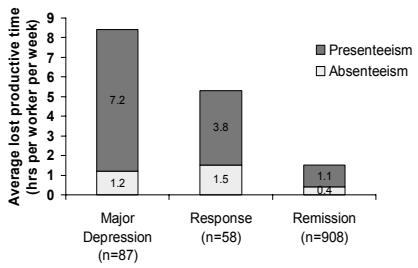
5 Simple Messages to Promote Medication Adherence

- **Take medication daily**
- **It may take 2 to 4 weeks to start noticing improvement**
- **Do NOT stop taking medication without talking to doctor, even if feeling better**
- **Mild side effects are common when starting treatment, and usually temporary**
- **Call with any questions**

Recommendation #6g – Acute Treatment

Only remission leads to full return of productivity

Majority of lost productivity is hidden by reduced performance while at work



US employed individuals participating in the American Productivity Audit and the Depressive Disorders sub-study (n=3351)
Adapted from Stewart WF, et al. JAMA.2003; 289:3135-3144.

Medication strategies for sub-optimal response to a first-line antidepressant

Response:	Intolerant due to GI side effects	Intolerant due to sexual side effects	No response*	Partial response* or Residual symptoms*
Medication strategies	▸ Switch to escitalopram ▸ Switch to bupropion ▸ Switch to mirtazapine	▸ Switch to bupropion ▸ Switch to mirtazapine	▸ Augment with Cytomel or atypical antipsychotic ▸ Switch to another first-line agent	▸ Augment or combine

Note: these recommendations are based on varying levels of evidence currently, but take into account probable efficacy and tolerability.

* Based on symptom rating scales