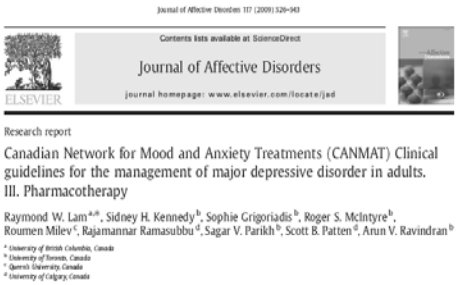
Psychopharmacology Update:
New Guidelines
New Drugs

Beth Sproule, PharmD
CMHCN Conference
February 20, 2010

Outline

- **New Guidelines**
  - **CANMAT** ***(Canadian Network for Mood and Anxiety Treatments)***
    - **Depression - October 2009**
    - **Bipolar Disorder Update - February 2009**
- **New Drugs**
  - **Acamprosate**
  - **Buprenorphine**

CANMAT Depression Guidelines



CANMAT Depression Guidelines 2009

- **First Line**
  - **SSRIs**
  - **SNRIs**
    - **desvenlafaxine**
    - **duloxetine**
    - **venlafaxine**
  - **mirtazapine**
  - **bupropion**
  - **moclobemide**
- **Second Line**
  - **TCAs**
  - **trazodone**
  - **quetiapine**
- **Third Line**
  - **MAOIs**

- **Duloxetine**
  - **Cymbalta®**
  - **comparable efficacy and tolerability to venlafaxine**
    - **more GI effects**
    - **less risk of hypertension**
  - **60 mg per day**
  - **also indicated for generalized anxiety disorder**
  - **covered under ODB**
- **Desvenlafaxine**
  - **Pristiq®**
  - **active metabolite of venlafaxine (via CYP2D6)**
  - **50 mg per day**
  - **minimal advantages – less pharmacokinetic drug interaction potential**
  - **not covered under ODB**

(Perahia 2008, Sproule 2008)

Quetiapine as Monotherapy

- **quetiapine XR 50 – 300 mg**
- **Level 1 evidence, approved indication in Canada, if other therapies fail**
- **magnitude of the treatment effect (placebo-subtracted difference) in the acute studies is comparable to conventional antidepressants, with suggestion of a faster onset of action**
- **major limitations:**
  - **weight gain**
  - **disrupted glucose/lipid homeostasis**
  - **sedation/somnolence**

(McIntyre 2009)

News

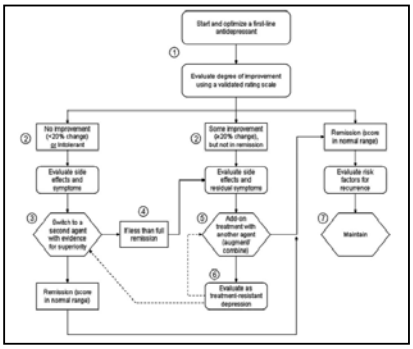
FDA advisers wary of expanding quetiapine use

Clinicians air concerns about metabolic effects, tardive dyskinesia

FDA advisers who met in April to discuss broadening the labeling of Seroquel XR, AstraZeneca's extended-release formulation of quetiapine fumarate, unanimously agreed that the drug should not be used as a first-line monotherapy for major depressive disorder (MDD) or generalized anxiety disorder (GAD).

"I just don't think that the long-term risks have been adequately characterized," said Duke University Medical School cardiologist Robert Harrington, 1 of 10 experts commissioned by FDA to vote on whether to expand the drug's labeling. Harrington was particularly concerned about metabolic effects associated with the drug's use, including weight gain, dyslipidemia, and blood-glucose abnormalities.

Depression Treatment Algorithm



(CANMAT Depression Guidelines 2009)

(McIntyre 2005)

CANMAT Depression Guidelines 2009

- ***How long do you wait for a clinical response?***
  - **onset of antidepressant effect can occur within 1-2 weeks**
    - **if <20% improvement in 2 weeks, make a change (e.g., increase dose)**
  - **response and remission may take longer**
    - **if > 20% improvement after 4-6 weeks, continue therapy another 2-4 weeks before changing**

Comparative Efficacy

Table 4
First-line antidepressants with evidence for superior efficacy against comparators.

Antidepressant	Comparators
Duloxetine [Level 2]	Paroxetine; pooled SSRIs
Escitalopram [Level 1]	Citalopram; duloxetine; paroxetine; pooled SSRIs
Milnacipran [Level 2]	Fluvoxamine; pooled SSRIs
Mirtazapine [Level 2]	Trazodone
Sertraline [Level 1]	Fluoxetine; pooled SSRIs
Venlafaxine [Level 1]	Duloxetine; fluoxetine; pooled SSRIs

(CANMAT Depression Guidelines 2009)

Recommendations for Non-Response

Table 11
Recommendations for non-response and incomplete response to an initial antidepressant.

• First-line	• Switch to an agent with evidence for superiority	• Duloxetine [Level 2] • Escitalopram [Level 1] • Milnacipran [Level 2] • Mirtazapine [Level 2] • Sertraline [Level 1] • Venlafaxine [Level 1]
	• Add-on another agent	• Aripiprazole [Level 1] • Lithium [Level 1] • Olanzapine [Level 1] • Risperidone [Level 2]
• Second-line	• Add-on another agent	• Bupropion [Level 2] • Mirtazapine/mianserin [Level 2] • Quetiapine [Level 2] • Triiodothyronine [Level 2] • Other antidepressant [Level 3]
	• Switch to an agent with evidence for superiority, but with side effect limitations	• Amitriptyline [Level 2] • Clomipramine [Level 2] • MAO Inhibitors [Level 2]
• Third-line	• Add-on another agent	• Buspirone [Level 2] • Modafinil [Level 2] • Stimulants [Level 3] • Ziprasidone [Level 3]

(CANMAT Depression Guidelines 2009)

Second Generation Antipsychotics as Add-On Treatment

- **Aripiprazole**
  - **Level 1 evidence, FDA approved**
  - **Augmenting SSRIs/SNRIs**
  - **2 – 20 mg/day (15 mg max if fluoxetine or paroxetine)**
- **Olanzapine**
  - **Level 1 evidence**
  - **Olanzapine-fluoxetine combination in treatment resistant depression**
  - **6 – 18 mg/day**

Second Generation Antipsychotics as Add-On Treatment

- **doses used as add-on treatment for MDD are usually lower than used for mania or schizophrenia**
- **Side-effect influence on risk-benefit assessment**
  - **Weight gain**
  - **Metabolic syndrome**
  - **EPS**
- **olanzapine > aripiprazole for metabolic risks**
- **aripiprazole not covered under ODB*****

Second Generation Antipsychotics Metabolic Monitoring

Table 4 ADA–APA consensus guidelines*

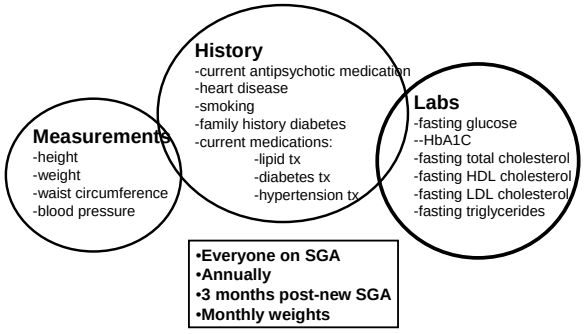
	Base	At 4 weeks	At 8 weeks	At 12 weeks	Every 3 months	Annual	Every 5 years
Medical history†	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipids	X			X			X

*From ADA-APA (32)
†Personal and family history of obesity, diabetes, hypertension, and cardiovascular disease

Cohen TA, Sernyak MJ. Metabolic monitoring for patients treated with antipsychotic medications. Can J Psychiatry 2006;51:492–501.

American Diabetes Association, American Psychiatric Association, et.al. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596–601.

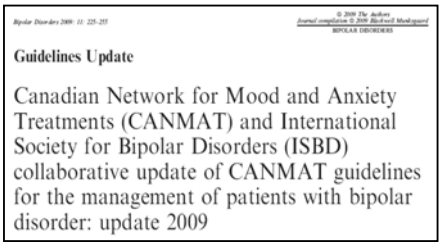
CAMH Metabolic Health Monitor



CANMAT Depression Guidelines 2009

- ***principles of pharmacotherapy management***
- ***emergent suicidality***
- ***differences in tolerability***
- ***differences in potential for drug-drug interactions***
- ***duration of therapy***
- ***use in pregnancy***
- ***use in children/adolescents***

Bipolar Disorder



2005 Original: Bipolar Disorders 2005;7(Suppl.3):5-69.
2007 Update: Bipolar Disorders 2006;8:721-739.
2009 Update: Bipolar Disorders 2009;11:225-255.

Treatment Goals in Bipolar Disorder

- Reduction in number and severity of episodes
- Improved inter-episode functioning
- Suicide prevention

Treatment Targets

- Acute mania
- Acute bipolar depression
- Prophylaxis, maintenance

Mood Stabilizers

	Lithium	Valproate	Carbamazepine	Lamotrigine
Mania	First	First	Second	Not Recommended
Depression	First	Second	Third	First
Maintenance	First	First	Second	First (Only if mild mania)

Atypical Antipsychotics

	Quetiapine	Olanzapine	Risperidone	Ziprasidone	Aripiprazole
Mania	First	First	First	First	First
Depression	First	Third	-	-	Not Recommended
Maintenance	First	First	First	-	First (preventing mania)

New Drugs

- Acamprosate
  - Alcohol dependence
- Buprenorphine
  - Opioid dependence

Pharmacotherapy of Addictions

- Medical Withdrawal (detoxification)
  - to prevent severe complications, particularly seizure activity
  - to provide support and reduce symptomatology to increase likelihood of successful withdrawal
- Addiction
  - maintain abstinence (relapse prevention)
  - reduce use – harm reduction
  - improve psychosocial outcomes (e.g., impact of drug use on employment, reconciliation with family members)

Pharmacotherapy of Alcohol Addiction

- Abstinence-promoting and relapse prevention therapies
  - Disulfiram (Antabuse®)
  - naltrexone (ReVia®)
  - acamprosate (Campral®)

Acamprosate

- now approved in Canada (Campral®)
  - has been available in Europe and US longer
- restores glutamate tone and modulates neuronal hyperexcitability following alcohol cessation
  - does not reduce withdrawal symptoms
- efficacy in abstinence rates and time to relapse
- may need several days of abstinence (e.g., 7 days) prior to starting to be most effective (not well worked out)

Acamprosate

- Dosage: 2 x 333mg tid (titrated up)
- Food decreases absorption
- Well tolerated: diarrhea mainly (self-limiting), headache
- Renally eliminated
  - ½ dose CrCl 30-50ml/min, avoid CrCl < 30
- Interaction with alcohol unlikely
- Not covered under ODB***

Pharmacotherapy of Opioid Addiction

- Opioid Substitution
  - methadone
  - naltrexone (ReVia®)
  - buprenorphine (Suboxone®)

Buprenorphine

- alternative to methadone for opioid substitution treatment
- partial agonist at *mu*-opioid receptors
- available as Suboxone®
  - sublingual tablets
  - buprenorphine 2 mg and 8 mg in fixed combination with naloxone 0.5 and 2 mg respectively
    - to deter injection drug use

Buprenorphine

- slow onset of action and extended duration of action
  - Kinetics: sublingual absorption
  - Dynamics: very tight binding to opioid receptors
- may be easier to taper than methadone
- associated with less stigma than methadone
- not covered under ODB***

Buprenorphine

- **Clinical implications of partial agonist activity**
  - **Safer in overdose: "ceiling effect"**
    - **Although respiratory depression still a concern, especially if combined with other CNS depressants**
  - **Lower potential for abuse**
    - **Although can still be abused**
  - **Can titrate to an effective dose more quickly**
  - **Maximal doses may not be sufficient**
    - **May need methadone for high dose requirements**

Precipitated Withdrawal	**Induction**
Relative to intoxication, **Suboxone®** "turns on" receptors less ∴ patient feels withdrawal	Relative to withdrawal, **Suboxone®** "turns on" receptors more ∴ patient feels better

Buprenorphine

- **CPSO requirements**
  - **Do not need an 'exemption' from Health Canada**
  - **Training/education in this drug, and addiction medicine generally**
    - **prescribing course in buprenorphine**
    - **one-day clinical observership**
    - **ongoing continuing medical education**
- **www.suboxonecme.ca**
- **www.camh.net/education**

Opioid Dependence Treatment CERTIFICATE PROGRAM

The Core Course meets the CPSO and OCP regulatory requirements for prescribing and dispensing methadone and buprenorphine for treatment of opioid dependence.

The **Certificate Program** has been approved as an 83.5-credit (CFPC) certificate program by the office of Continuing Education, Faculty of Medicine, University of Toronto.

The courses are approved for CACCF CEC hours.

For more information about this program, please call

1 800 661-1111 or

416 535-8501, ext. 6640.

Description

The Opioid Dependence Treatment Certificate Program has been developed to prepare physicians, pharmacists, nurses and counsellors to assess and treat people with opioid dependence.

This program uses a blended learning approach that includes online and classroom components.

Courses

Participants interested in obtaining a Certificate in Opioid Dependence Treatment should complete the Core Program plus three or four elective courses (total of 39+ hours).

Core course (required)
11.5 Mainpro-M1 credits, and recognized for 11 CE credits through the Ontario College of Pharmacists
- Five self-directed online modules

followed by
- A one-day workshop

Elective courses (select three or four)
- Advanced Issues in Methadone Maintenance Treatment
  3.5 Mainpro-M1 credits
- Introduction to Motivational Interviewing
  11.5 Mainpro-M1 credits
- Advanced Strategies in Motivational Interviewing
  12 Mainpro-M1 credits
- Introduction to Concurrent Disorders (Online course)
  14 Mainpro-M1 credits
- Basic Pharmacology in Mental Health and Substance Use (Online course)
  11 Mainpro-M1 credits
- Interactions between Psychiatric Medications and Substances of Abuse (Online course)
  14 Mainpro-M1 credits

For more INFORMATION or to REGISTER, please visit our website at http://www.camh.net/education

camh | Education Services

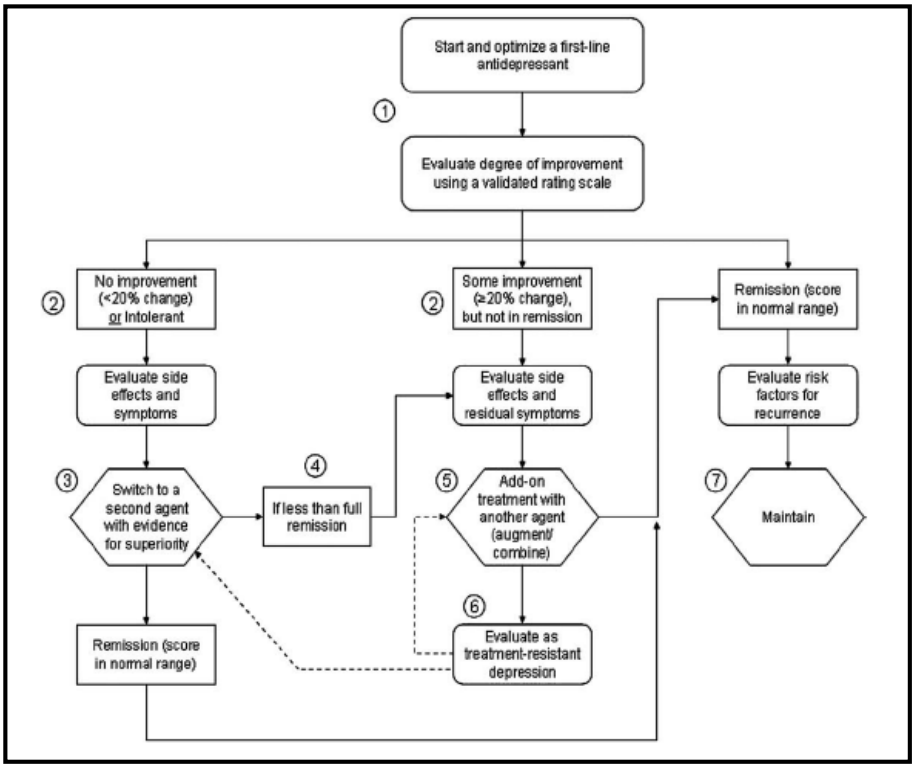
References

- **Lam RW, et.al., Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines For the management of major depressive disorder in adults. III. Pharmacotherapy. Journal of Affective Disorders 2009;117:S26-S43.**
- **McIntyre RS, et.al., Quetiapine XR efficacy and tolerability as monotherapy and adjunctive treatment to conventional antidepressants in the acute and maintenance treatment of major depressive disorder: a review of registration trials. Expert Opin Pharmacother 2009;10(18):3061-3075.**
- **Perahia D, et.al., A randomized, double-blind comparison of duloxetine and venlafaxine in the treatment of patients with major depressive disorder. Journal of Psychiatric Research 2008;42:22–34.**
- **Sproule BA, Hazra M, Pollock BG. Desvenlafaxine succinate for major depressive disorder. Drugs of Today 2008;44(7):475-487.**
- **McIntyre RS, et.al., Measuring the severity of depression and remission in primary care: validation of the HAMD-7 scale. Canadian Medical Association Journal 2005;173(11):1327-1334.**

References

- **Reynolds & Kirk. Metabolic side effects of antipsychotic drug treatment – pharmacological mechanisms. Pharmacology & Therapeutics 2010;125:169–179.**
- **Yatham LN, et.al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disorders. 2009; 11:225-255.**
- **Yatham LN, et.al. CANMAT. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disorders. 2006; Dec;8(6):721-39.**
- **Yatham LN, et.al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disorders 2005;7(Suppl 1):5-69.**
- **Carmen B, et.al., Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction 2004;99:811–828.**
- **Isaac P, Janecek E, Kalvik A, Sproule B. Buprenorphine: A new treatment for opioid dependence. OCP Pharmacy Connections 2008; Jan/Feb:32-37.**

Depression Treatment Algorithm



(CANMAT Depression Guidelines 2009)

Recommendations for Non-Response

Table 11
Recommendations for non-response and incomplete response to an initial antidepressant.

• First-line	• Switch to an agent with evidence for superiority	• Duloxetine [Level 2] • Escitalopram [Level 1] • Milnacipran [Level 2] • Mirtazapine [Level 2] • Sertraline [Level 1] • Venlafaxine [Level 1]
	• Add-on another agent	• Aripiprazole [Level 1] • Lithium [Level 1] • Olanzapine [Level 1] • Risperidone [Level 2]
• Second-line	• Add-on another agent	• Bupropion [Level 2] • Mirtazapine/mianserin [Level 2] • Quetiapine [Level 2] • Triiodothyronine [Level 2] • Other antidepressant [Level 3]
	• Switch to an agent with evidence for superiority, but with side effect limitations	• Amitriptyline [Level 2] • Clomipramine [Level 2] • MAO Inhibitors [Level 2]
• Third-line	• Add-on another agent	• Buspirone [Level 2] • Modafinil [Level 2] • Stimulants [Level 3] • Ziprasidone [Level 3]

(CANMAT Depression Guidelines 2009)

Opioid Dependence Treatment CERTIFICATE PROGRAM

The Core Course meets the CPSO and OCP regulatory requirements for prescribing and dispensing methadone and buprenorphine for treatment of opioid dependence.

The **Certificate Program** has been approved as an 83.5-credit (CFPC) certificate program by the office of Continuing Education, Faculty of Medicine, University of Toronto.

The courses are approved for CACCF CEC hours.

For more information about this program, please call

1 800 661-1111 or

416 535-8501, ext. 6640.

Description

The Opioid Dependence Treatment Certificate Program has been developed to prepare physicians, pharmacists, nurses and counsellors to assess and treat people with opioid dependence.

This program uses a blended learning approach that includes online and classroom components.

Courses

Participants interested in obtaining a Certificate in Opioid Dependence Treatment should complete the Core Program plus three or four elective courses (total of 39+ hours).

Core course (required)

11.5 Mainpro-M1 credits, and recognized for 11 CE credits through the Ontario College of Pharmacists

- Five self-directed online modules

followed by

- A one-day workshop

Elective courses (select three or four)

- Advanced Issues in Methadone Maintenance Treatment
  3.5 Mainpro-M1 credits
- Introduction to Motivational Interviewing
  11.5 Mainpro-M1 credits
- Advanced Strategies in Motivational Interviewing
  12 Mainpro-M1 credits
- Introduction to Concurrent Disorders (Online course)
  14 Mainpro-M1 credits
- Basic Pharmacology in Mental Health and Substance Use (Online course)
  11 Mainpro-M1 credits
- Interactions between Psychiatric Medications and Substances of Abuse (Online course)
  14 Mainpro-M1 credits

For more INFORMATION or to REGISTER, please visit our website at http://www.camh.net/education

camh
Centre for Addiction and Mental Health
Centre de toxicomanie et de santé mentale
Education Services