

What's new in Mental Health?



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SERHA (RHA B)
- CSHP-NB AGM 2008
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- Countdown to delivery:
155 days

Objectives

- Highlight new medications available for treating mental illness, including duloxetine (Cymbalta®) and ziprasidone (Zeldox®).
- Assess options for switching pharmacological treatment for psychosis and depression
- Review risks and benefits of smoking cessation options with respect to patients with mental illness.

Case 1

- LB has recently started treatment with paroxetine (titrated to 40 mg/d over 2 months) for an episode of MDD. She notes improvement in some symptoms such as sleep and anxiety but wishes to achieve greater improvement in her mood. As well, she has experienced decreased libido since starting paroxetine. LK inquires about the benefits of Cymbalta® (duloxetine).

duloxetine

- New antidepressant available in Canada
- Indicated for major depressive disorder (MDD) and neuropathic pain associated with diabetic peripheral neuropathy
- Acts as a SNRI, similar to venlafaxine (serotonin and norepinephrine)

duloxetine

- Taken once daily (60 mg)
- Very important to take with food initially
- Marketing: fast onset, immediate dual action, low incidence sexual dysfunction
- Substrate of: 2D6 and 1A2
- Inhibitor of: 2D6 (moderate), 1A2 (potential, based on in vitro studies)

Duloxetine: drug interactions

Drug	Effect	Mechanism
Fluvoxamine	↑ duloxetine	1A2 inhibition
Ciprofloxacin	↑ duloxetine	1A2 inhibition
Paroxetine	↑ duloxetine	2D6 inhibition
Triptans	Serotonin syndrome	Additive effect
Warfarin	↑ INR	Not stated
Smoking	↓ duloxetine	? 1A2 induction
Alcohol	Liver injury	?

Efficacy vs. antidepressants

- **SNRI vs. SSRI:** No studies adequately powered to detect differences between paroxetine and duloxetine.^{10,11,12}
- **SNRI vs. SNRI:** More patients treated with venlafaxine (150 mg/d) completed the study ($P \leq 0.038$) and more patients treated with duloxetine (60mg/d) experienced adverse effects ($P < 0.032$)¹³

Efficacy: paroxetine vs duloxetine

Study	Outcome	Results
Detke 2004 ¹⁰	Response rate (50% ↓ HAMD) at 8 wks	Placebo 44%
		Duloxetine 80 mg/d 65%
		Duloxetine 120 mg/d 71%
		Paroxetine 20 mg/d 74%
Goldstein 2004 ¹¹	Total HAMD score (8 wks)	Duloxetine 80 mg/d more effective than paroxetine 20 mg/d; caution re: <u>dose</u> and lack of power
Perahia 2006 ¹²	Change in HAMD (8 wks)	Both doses of duloxetine (80 and 120 mg/d) better than placebo ($P < 0.05$); paroxetine no sig. diff from placebo ($P = 0.089$)

Tolerability: sexual dysfunction

Detke ¹⁰	8 weeks	Duloxetine 46.5% Paroxetine 62.8% (P=NS)
Goldstein ¹¹	8 weeks	Placebo 16.7% Duloxetine 28.6% Paroxetine 34.4% (P=NS)
Perahia ¹²	8 weeks	Placebo 9.6% Duloxetine 80 mg/d 63.1%** Duloxetine 120 mg/d 30.1% Paroxetine 64.1%** P<0.05, vs. placebo
Perahia ¹²	6 months	Placebo 24.7% Duloxetine 80 mg/d 25% Duloxetine 120 mg/d 20.7% Paroxetine 24.7%

Tolerability: duloxetine

- Common adverse effects include:
 - Nausea (take with food!)
 - Insomnia
 - Dizziness
- Caution with elevated blood pressure and liver dysfunction, alcohol use

Making the switch...

- To switch from a SSRI to a SNRI, no washout is required but a taper is recommended.⁹
- Should decrease the 1st drug over 3-7 days, then initiate the 2nd drug (consider lower dose).
- Individualize based on individual concern of relapse, intolerance, safety.

Making the switch...

- Consider (not only 1 way to make switch):
 - ↓ paroxetine to 30 mg/d for 3 days
 - ↓ paroxetine to 20 mg/d + duloxetine 30 mg/d (reduced dose) for 7 days
 - Discontinue paroxetine and ↑ duloxetine to 60 mg/d.
- Monitor for serotonin side effects (e.g. nausea, vomiting, ...)

Case 2

➤ DM is a 45 year male with a history of paranoid schizophrenia. He is currently treated with olanzapine (30 mg/d); recent blood work reveals elevated glucose (Hb_{A1C}=7.9%; FPG=7.4mmol/L) and cholesterol (total=6.2 mmol/L; LDL=4.5mmol/L; TG=1.97mmol/L). Though DM's symptoms improved, his psychiatrist wishes to change treatment to ziprasidone due to metabolic concerns.

ziprasidone

- New atypical antipsychotic available in Canada
- Indicated for treatment of schizophrenia and related psychotic disorders
- Dosed twice daily (40-160 mg/d)
- Less weight gain and risk of increased cholesterol
- Can increase QT_c interval—significance??

ziprasidone

Adverse effects:

- Somnolence (14%)
- Extrapyramidal side effects (14%)
- Respiratory tract infection (8%)
- Hypotension
- Dry mouth
- Dizziness

ziprasidone

- Mechanism
 D₂ and 5HT₂ antagonism (therapeutic effect)
 H₁ antagonism (somnolence)
 α₁ antagonism (orthostatic hypotension)
- Drug interactions
Substrate: 3A4 and 1A2 (minor pathway)

Ziprasidone: drug interactions

Drug	Effect	Mechanism
Carbamazepine	↓ ziprasidone	3A4 induction
Valproate, lamotrigine	?	Not studied
Oral contraceptive	No effect	Note: only 40 mg/d studied
Lithium	No effect	Consider cardiac conduction changes
Alcohol	Additive sedation	Caution with CNS depressants
smoking	No significant effects	Consider 1A2 pathway minor

Efficacy: olanzapine vs. ziprasidone

- Studies ranging from 6-28 weeks indicate comparable efficacy between olanzapine and ziprasidone with a trend toward greater efficacy for olanzapine treatment
- Results dependent on dose (OLZ 15 or 20 mg/d), sponsor (Lilly vs. Pfizer), and outcome (depressive symptoms).^{1,2,3,4}

Safety: olanzapine vs. ziprasidone

➤ **Glucose**

Short studies (6-8 weeks): olanzapine group experiences increased insulin levels or Hb_{A1C}.^{1,4}

Longer studies (28 wks): NO significant difference between olanzapine and ziprasidone.^{2,3}

Case reports: Diabetes associated with ziprasidone⁵ and olanzapine-induced hyperglycemia resolving after switch to ziprasidone reported.⁶

Safety: olanzapine vs. ziprasidone

➤ **Cholesterol**

Significant increases in cholesterol, triglycerides, and weight have been observed with olanzapine (vs. ziprasidone).^{1,2,3,4}

Significant decreases in total cholesterol and triglycerides were observed 6 weeks after switch to ziprasidone from other antipsychotics, independent of weight changes (n=37).⁷

Safety: Cardiac Risk

➤ A 6 week, double-blind trial reported that MEN treated with olanzapine had a mean increase of 7.69% in their Framingham risk score (FRS) vs. a decrease of 11% in patients treated with ziprasidone. (P=0.09).

➤ Women did **not** demonstrate a significant difference, though there was a trend favoring treatment with ziprasidone.⁸

Making the switch...

4 options⁹

- Washout/start: increased risk of relapse
- Stop/start: risk of relapse and withdrawal symptoms. Consider if serious adverse effect from drug #1.
- **Cross-taper** over 1-4 weeks: increased risk of adverse effects; can be expensive.
- Delayed withdrawal: Start 2nd drug (therapeutic dose) prior to decreasing 1st drug

Another atypical antipsychotic: paliperidone (Invega®)

➤ Active metabolite of risperidone; No direct comparisons to risperidone.

➤ Available as oral tab; IM (depot) formulation in future?

➤ Efficacy: doses greater than 3 mg/d comparable to olanzapine 10 mg/d¹⁶

➤ ↑ tachycardia and ↑ prolactin compared to placebo

➤ Less weight gain than olanzapine

Back to DM

➤ Cardiac risk factors:

- | | |
|----------------------|---|
| 1) Male gender | X |
| 2) Increased age | |
| 3) Diabetes | X |
| 4) Smoking status | X |
| 5) Cholesterol level | X |

Options for smoking cessation

- 'Cold turkey'
- Nicotine replacement
- Varenicline (Champix®)

Cigarette smoking

- Can induce CYP 1A2⁹
- Decrease clozapine* levels by _____%
- Decrease olanzapine levels by _____%

Caution if client stops smoking during therapy. Increased risk of toxicity from antipsychotic agent.

*clozapine levels not routinely ordered

Varenicline (Chantix®)

- NOT tested in patients with mental illness
- By Nov 2007, Health Canada had received notice of **46** psychiatric adverse reactions attributed to varenicline.¹⁵
- **Fourteen** of these included **depression and suicidal** thinking or tendencies. In some cases, the patient had a history of depression.¹⁵

Varenicline (Champix®)

- **Public Health Advisory**
Important Information on Chantix (varenicline)
- FDA is issuing this public health advisory to alert patients, caregivers, and healthcare professionals to important changes to Chantix prescribing information. Chantix is a medicine used to help patients stop smoking.
- At the request of FDA, Pfizer, the manufacturer of Chantix, has updated the Chantix prescribing information to include warnings about the possibility of severe changes in mood and behavior in patients taking Chantix. FDA is highlighting the following related important safety information on Chantix:
- **Patients should tell their doctor about any history of psychiatric illness prior to starting Chantix.** Chantix may cause worsening of a current psychiatric illness even if it is currently under control and may cause an old psychiatric illness to reoccur.

<http://www.fda.gov/cder/drug/advisory/varenicline.htm> (last accessed May 13, 2008)

Varenicline (Chantix®)

- **Healthcare professionals, patients, patients' families, and caregivers should be alert to and monitor for changes in mood and behavior in patients treated with Chantix.** Symptoms may include anxiety, nervousness, tension, depressed mood, unusual behaviors and thinking about or attempting suicide. **In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of varenicline therapy.**
- **Patients taking Chantix should immediately report changes in mood and behavior to their doctor.**
- **Patients taking Chantix may experience vivid, unusual, or strange dreams.**
- **Patients taking Chantix may experience impairment of the ability to drive or operate heavy machinery.**
- **While Chantix has demonstrated clear evidence of efficacy, it is important to consider these safety concerns and alert patients that they are possible.**

<http://www.fda.gov/cder/drug/advisory/varenicline.htm> (last accessed May 13, 2008)

Summary

- New options for treatment of:
 - **Depression:** duloxetine
 - **Psychosis:** ziprasidone, paliperidone
- Switching treatment requires individual approach
- Patients with mental illness may not be included in trials assessing new meds—caution.

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Thank you!

