

## What's New and Exciting in Psychiatry

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## New Releases in Canada

- 1990 – Clozapine
- 1994 – Risperidone
- 1996 – Olanzapine
- 1997 – Quetiapine
- Since then ...
  - Oral dissolvable formulations (“melt in your mouth AND in your hands”) Risperidone and Olanzapine
  - Short acting IM Olanzapine
  - Long acting depot IM Risperidone
  - SR formulation Quetiapine

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## Waiting for something new in the treatment of Schizophrenia

...



Clinical  
Pharmacist ...

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## 10 years later... in 2007

- Health Canada issues a Notice of Compliance for 2 new second generation (atypical) antipsychotics
  - Ziprasidone (Zeldox®)
  - Paliperidone (Invega®)
- Is it time to cue the fireworks??



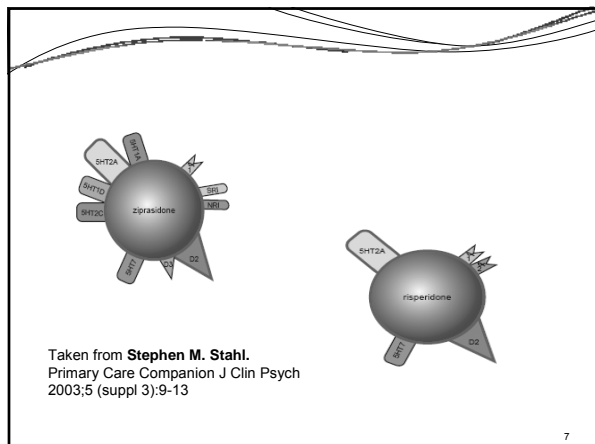
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## Antipsychotic Pharmacology Review

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Receptor action	The Good	The Bad
D2 Blockade	Antipsychotic effect	EPS (tremor, rigidity, akinesia, postural instability), Elevated Prolactin, Sexual Dysfunction, Akathisia
5HT-2a Blockade	Antipsychotic effect May decrease EPS Some Anxiolytic, Antidepressant and Antimigraine effects	Hypotension Sedation Sexual Dysfunction Obsessions and compulsions
Muscarinic Blockade “anticholinergic”	Antiparkinson effect	Dry mouth, blurred vision, Constipation, Urinary retention, Drowsiness, Memory problems
Alpha-1 Blockade		Hypotension, Dizziness, Tachycardia, Sexual dysfx
Histamine Blockade	Antiemetic effect	Sedation, Hypotension, Weight gain

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## Scales for outcomes measurement

- Brief Psychiatric Rating Scale (BPRS)
  - 18 items, each rated on a 7-point scale
  - Unstructured 15-20 minute interview
  - Total score range = 18-126
- Positive and Negative Syndrome Scale (PANSS)
  - 30 items, each rated on a 7-point scale
  - Semi-structured 30-50 minute interview
  - Total score range = 30-210
- Clinical Global Impression (CGI)
  - A single 7-point scale

Matza LS et al. CNS Drugs 2005;19(6):499-515

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## Ziprasidone Review

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## Ziprasidone HCl

- Marketed as Zeldox® in Canada (Geodon® in US)
  - Oral formulation only (US has short-acting IM)
- Indications: treatment of schizophrenia and related psychotic disorders.
- Pharmacology: Receptor BLOCKADE
  - Strong: 5HT-2a receptors > D2 receptors
  - Moderate: Alpha-1 (α1) receptors
  - Minimal-None: Muscarinic (M1) receptors
  - Minimal: Histaminic (H1) receptors

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## Ziprasidone Pharmacokinetics

- Well absorbed orally – should be taken WITH food
- In doses of 20 – 80 mg bid
  - Tmax = 3.8-4.7 hrs
  - T ½ = 4.8 – 10 hrs
- Steady state reached in 1-3 days
- Highly protein bound (>99%) to albumin, α1-acid-glycoprotein
- Extensively metabolized by liver
  - Mainly via reduction by aldehyde oxidase
  - Lesser extent by CYP P450 (3A4, 1A2)

Swainston T, CNS Drugs 2006;20(12):1027-52

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## Side effect profile

- EPS (similar to Risperidone)
- Elevated prolactin
- Orthostatic hypotension (less than Risperidone)
- Minimal to No anticholinergic effects
- Less sedation and weight gain than other atypicals
  - Considered weight neutral
  - Low incidence of metabolic changes
- Potential for QT prolongation (more than other atypicals)
  - Contraindicated in pts with prolonged QT, recent acute MI, uncompensated heart failure

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## Dosing

- Available as 20, 40, 60 and 80 mg
- Start with 20-40 mg BID with food and increase q2days to a maximum of 80 mg BID with food

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## Drug interactions

- Coadministration with CYP 3A4 inducers (carbamazepine) or inhibitors (ketoconazole) do affect the AUC and Cmax of Ziprasidone
  - Monograph states dosage adjustments are not required due to the alternative metabolic pathway
- No in vitro changes to protein binding of warfarin or propranolol or ZIP
- No interaction with lithium or oral contraceptives (with ZIP 40-80 mg/day)
- Drug-food interaction – when taken with food it doubles the absorption of ZIP

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## Clinical trial data

- Cochrane Systematic Review 2000
  - Included 7 studies, Short-term data (1-6 wks), high attrition rates
  - Improvement defined as
    - 1-2 point improvement on CGI, 30% reduction of PANSS or BPRS total score from baseline
  - Versus Placebo
    - RR 0.8 (CI 0.7-0.9) SS, no difference in wt gain vs placebo
  - Versus Haloperidol
    - RR 0.8 (CI 0.7-1.0) NS
    - Less likely to cause movement disorders, more likely to cause n/v

Bagnall A et al. Cochrane Systematic Review 2000, Issue 4. Art No CD001945

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## ZIP vs Placebo

- 1 yr trial, n= 278
- 40 mg, 80 mg, 160 mg/d vs PBO
- 50 yr pts with chronic schizophrenia
- Baseline PANSS 86
- Relapse rates at 1 yr
  - Zip 40 mg/d = 43%
  - Zip 80 mg/d = 35%
  - Zip 160 mg/d = 36%
  - PBO = 77% (all SS vs PBO)

Arato M et al. ZEUS study. Int Clin Psychopharmacol 2002;17:207-15

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## Ziprasidone vs Atypicals

- Versus Risperidone (1 study)
  - Addington DEN et al. J Clin Psych 2004;65(12):1624-1633
- Versus Olanzapine (4 studies)
  - Simpson GM et al. Am J Psych 2004;161(10):1837-47
  - Harvey PD et al. Psychopharmacology 2004;172:324-32 (cognitive assessment of above trial)
  - Simpson GM et al. Am J Psych 2005;162(8):1535-38 (6 mo extension)
    - Harvey PD et al. J of Neuropsych Clin Neurosci 2006;18:54-63 (cognitive ass't)
  - Breier A et al. Am J Psych 2005;162(10): 1879-87
  - Kinon BJ et al. J Clin Psychopharmacol 2006;26(2):157-62
- ALL industry sponsored by either Eli Lilly or Pfizer
- Versus Perphenazine, Olanzapine, Risperidone and Quetiapine (CATIE I and II trials) – government sponsored

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## ZIP vs RISP

- N= 296, 8 weeks, DB, Equivalence trial in schizophrenia
- Primary outcome: change in total PANSS from baseline
- Mean age 34 yrs, Baseline PANSS 94-98 (mod-severe)
- Mean daily doses
  - Risperidone 7.4 mg
  - Ziprasidone 114.2 mg
- Results – met the criteria for equivalence
  - Discontinuation rates: in 37% ZIP, 29% Risp

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## ZIP vs OLZ

- 6 week trial with 6 month extension (funded by Pfizer)
- Equivalence trial, n= 269
- Mean age 37 yrs, Baseline PANSS 90
  - ZIP 129.9 mg/d at 6 wk; 135.2 mg/d at 6 mo
  - OLZ 11.3 mg/d at 6 wk; 12.6 mg/d at 6 mo
- Primary endpoint: Change to BPRS & CGI similar at 6 wks and within equivalence margin (also similar at 6 mo, change in PANSS similar -35 pts)
  - Discontinuation rates at 6 mo: OLZ 70.4%, ZIP 69%
- AE: Similar EPS, wt gain OLZ 3.5kg, QTc change ZIP 6 msec

Simpson GM 2004 and 2005; Harvey 2004 and 2006

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## ZIP vs OLZ

- 28 wk trial (funded by Lilly)
- Superiority trial, n = 548
- Mean age 38-40 yrs, baseline PANSS 100
- Mean dose
  - ZIP 116 mg/d
  - OLZ 15.3 mg/d
- Primary outcome reduction PANSS: OLZ 35.7 > ZIP 26 (ss)
  - Pts completing study: OLZ 59.6%, ZIP 42.4% (ss)
- OLZ wt gain 3 kg, ZIP insomnia and vomiting
- NS diff for QTc changes -5 msec each

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## ZIP vs OLZ

- 24 wk study in pts with prominent depressive sx (funded by Lilly)
- n= 394
- Mean age not reported ! Baseline PANSS 79; moderate depression MADRS 27; 50% on previous antidepressant tx
- Fixed dose grps: ZIP 80, 120, 160 mg/d; OLZ 10, 15, 20 mg/d
- Primary endpoint Calgary Depr Scale at 8 wks: NS diff
- Completers: OLZ 45%, ZIP 30%

Lieberman JA et al. J Clin Psych 2006;163(1):15-22

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## CATIE trial

(Clinical Antipsychotic Trials of Intervention Effectiveness)

- Largest 'real-world' effectiveness trial
- Government funded
- n= 1493, Baseline PANSS 75, mean age 40 yrs
- Primary endpoint: time to all-cause discontinuation
- Patients followed up to 18 months
- Phase 1: Comparing perphenazine, olanzapine, risperidone, quetiapine and ziprasidone
  - Phase 2T: OLZ, QTP, RISP, ZIP
  - Phase 2E: open-label clozapine, OLZ, RISP, QTP

Lieberman JA et al. NEJM 2005;353(12):1209-23.  
Stroup TS et al. Am J Psych 2006;163(4):611-22

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## CATIE results

- Fewer pts enrolled to Perphenazine and Ziprasidone arms (decreased power to detect differences)
- Mean daily doses
  - OLZ 20 mg, QTP 543 mg, RISP 3.9 mg, PER 20.8 mg, ZIP 113 mg
- Discontinuation rates / median time to d/c
  - OLZ 64% / 9.2 mo (6.9-12.1 mo) \* ss vs QTP and RISP
  - QTP 82% / 4.6 mo (3.9-5.5)
  - RISP 74% / 4.8 mo (4-6.1)
  - PER 75% / 5.6 mo (4.5-6.3)
  - ZIP 79% / 3.5 mo (3.1-5.4)

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## CATIE results ...

- Phase 2T – randomized to agent not received in Phase 1
  - 2:1:1:1 ratio to increase ZIP exposure
- N = 444
- Mean daily doses
  - OLZ 20.5 mg, QTP 565 mg, RISP 4.1 mg, ZIP 116 mg
- Median Time to discontinuation
  - OLZ 6.3 mo (3.5-9.7) \*ss vs QTP and ZIP
  - QTP 4.0 mo (3.1-4.8)
  - RISP 7 mo (4.1-10) \* ss vs QTP and ZIP
  - ZIP 2.8 mo (2.4-4.4)

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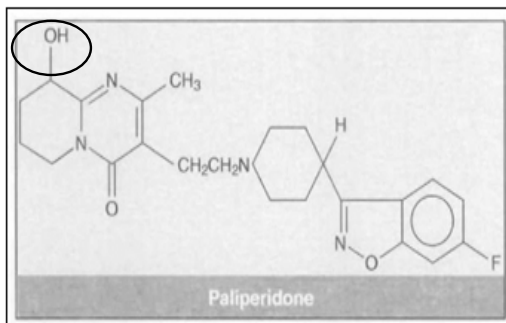
## CATIE Adverse Effects

- NS diff for EPS – more pts stopped PER due to EPS
- Weight change: increased with OLZ (9 lb); minimal increase with RISP and QTP (1 lb), minimal decrease with ZIP and PER (2 lb)
- Insomnia higher with ZIP and PER
- Prolonged QTc – QTP and RISP 3%; ZIP and PER 1%, OLZ none

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## Paliperidone Review

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Paliperidone Extended Release.

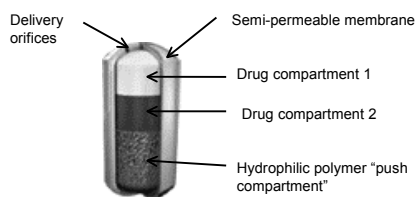
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## Paliperidone

- Marketed as Invega® in Canada
- Risperidone is metabolized by CYP 2D6 to a major active metabolite (9-OH risperidone) = Paliperidone
- Indications: approved for the treatment of schizophrenia
- Pharmacology: same receptor blockade profile as Risperidone
  - D2 and 5HT-2a blockade
  - $\alpha$ 1 and 2 blockade
  - Minimal H1 blockade

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## Paliperidone ER: via OROS® (Osmotic-controlled Release Oral-delivery System)



Other drugs to use OROS® mechanism:  
Concerta® (methylphenidate), Ditropan XL® (oxybutynin)

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## Paliperidone Pharmacokinetics

- Oral bioavailability 28%
- T<sub>max</sub> = 24 hrs
- Elimination t<sub>1/2</sub> = 23 hrs (with CrCl < 30 ml/min t<sub>1/2</sub> 51 hrs)
- Time to steady state = 4-5 days
- Protein binding 74% (mainly albumin and  $\alpha$ 1-acid glycoprotein)
- 80% renally cleared
- Unlike risperidone, paliperidone is NOT metabolized by CYP 2D6 – no drug interactions

Yang LPH. CNS Drugs 2007;21(5):417-25.

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## Dosing

- Available as 3, 6, 9 and 12 mg
- Swallowed whole (not chewed and crushed)
- Recommended starting dose is 6 mg daily with or without food
  - 3 mg daily for patients with CrCl < 50 mL/min
- Dosage adjustments by 3 mg daily every 5 days

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## Side effects

- Dose related: somnolence, orthostatic hypotension, tachycardia, EPS and hypersalivation
- Reports of prolonged QTc, neuroleptic malignant syndrome (potential with all antipsychotics)
- Similar to risperidone

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## Clinical trial data

- Three 6-wk placebo controlled trials done – reported in a pooled analysis
- N= 1326
- Mean age 38 yrs, baseline PANSS 93
- Five fixed-dose paliperidone ER active treatment groups (3, 6, 9, 12 or 15 mg)
- “Positive control” – Olanzapine 10 mg daily
  - To confirm assay sensitivity; not for comparison with paliperidone arm
- Primary endpoint: change in PANSS from baseline

Meltzer HY. J Clin Psych 2008;69(5):817-29.

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## PAL vs PBO ...

- Results
  - Improvements in PANSS from baseline in all grps paliperidone compared to placebo (\*ss)
  - PANSS improved by 15-20 points
  - Meet criteria for response
    - PAL 3 mg 39%, PAL 6 mg 53%, PAL 9 mg 48%, PAL 12 mg 57%, PAL 15 mg 53%; PBO 27%
- Adverse effects
  - EPS similar to PBO for 3 and 6 mg (10-13%) higher for 9-15 mg (25%)
  - Higher orthostatic hypotension 4% at higher doses vs 1-2 %

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## PAL for Relapse Prevention

- 8 wk run-in phase as in-pts – open label PAL until stable (n=530)
- 6 wk open label stabilization phase (outpt) (n=312)
- Randomized to double-blind PAL or PBO for up to 1 yr (n=207)
- Primary endpoint: time to first recurrence
- Mean age 39-41 yrs, baseline PANSS 55
- Mean daily dose = 10.8 mg
- Interim analysis – trial stopped early (as pre-determined stopping threshold was reached)

Kramer M. J Clin Psychopharmacol 2007;27(1):6-

14.

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## Relapse prevention ...

- Interim analysis – recurrence: PBO 53%, PAL 25%
- Final analysis – recurrence: PBO 52%, 22%
- Median time to recurrence (1/2 pts had a recurrence): PBO 62 days, PAL not estimable as 1/2 pts had not had a recurrence yet
- Adverse effects
  - Orthostatic hypotension, EPS, prolactin elevation (greater in women), weight gain > 7%: PBO 12%, PAL 20%

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## Place in Therapy for Ziprasidone and Paliperidone

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## Summary

- Schizophrenia is a chronic, difficult to treat illness
- No single treatment of choice
- Ziprasidone has head-to-head clinical data which suggests it has 'somewhat' comparable efficacy to other atypicals
  - Consider cardiac risk factors of the patient
  - Possible option for pts who have failed other agents and with metabolic side effects
- Paliperidone does not have head-to-head data
  - Fewer drug interactions and serum level variation compared to risperidone (possible improved SE profile)
  - Not yet convinced that it will 'replace' risperidone in therapy<sup>38</sup>

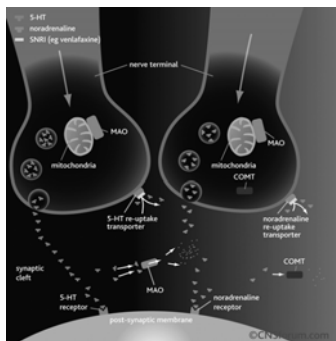
## Duloxetine Review

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## Duloxetine HCl

- Marketed as Cymbalta® in Canada
- **Indications:** Approved for the symptomatic relief of major depressive disorder (MDD) and for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN)
- **Pharmacology:** Selective Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)
  - Binding to NE > 5HT reuptake transporters
  - Lacks significant activity at D2,  $\alpha$ -1,2, muscarinic, histaminic and opioid receptors

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## Duloxetine Pharmacokinetics

- Well absorbed orally, not significantly affected by food
  - T<sub>max</sub> 6 (10 hrs with food)
- Elimination t<sub>1/2</sub> = 8-17 hrs
  - Time to steady state = 3 days
- Large volume of distribution – highly protein bound (>90%) to albumin and  $\alpha$ 1-acid glycoprotein
- Extensively metabolized via CYP 2D6 and 1A2 to form multiple inactive metabolites (excreted in urine)
  - Duloxetine inhibits CYP 2D6 (risperidone, TCA's, phenothiazines, type 1C antiarrhythmics)
  - Fluvoxamine, Ciprofloxacin, 1A2, Cigarette smoking induces

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## Dosing and Cautions

- Available as delayed-release capsules: 30 and 60 mg
- Recommended daily dose is 60 mg once daily
  - May start with 30 mg daily for improved tolerability and increase to 60 mg daily
- Contraindicated in severe liver disease and in patients with severe renal impairment
  - In pts who consume excessive alcohol – risk for liver injury
- Should not be used with MAOI's or Linezolid
- Avoid in uncontrolled narrow angle glaucoma

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## Side Effects

- Nausea
- Dry mouth
- Constipation
- Insomnia (fatigue, somnolence also reported)
- Dizziness
- Increased sweating
- Decreased appetite
- Sexual dysfunction (46% vs 29% with placebo)
- Only modest effects on HR and BP

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## Clinical trial data

- ALL industry sponsored
- 6 of 8 Registration trials vs placebo (PBO) looking at HAM-D scores at 8-9 weeks showed superiority of Duloxetine (DUL) over PBO<sup>1</sup>
  - Most of these trials included a "positive control" arm with either paroxetine or fluoxetine
  - not powered to compare DUL with the SSRI only vs. PBO
- 3 head-to-head trials vs. Escitalopram (ESC)
  - Response outcomes using HAM-D scores at 2 and 8 wks
    - DUL 60 mg vs ESC flex dosing 10-20 mg – inferior to ESC<sup>2</sup>
    - DUL 60 mg vs ESC 10 mg fixed dosing -- non-inferior to ESC<sup>3</sup>

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## Clinical trials ...

- 2 head-to-head trials vs Venlafaxine XR (VEN)<sup>5</sup>
  - Outcomes of Global Benefit-Risk (GBR)
  - 12 wk trials, DUL 60 mg and VEN 75-150 mg for first 6 wks, could titrate up to DUL 120 mg and VEN 225 mg for last 6 wks
  - DUL did NOT meet the non-inferiority criteria to VEN
- Meta-analysis of DUL and VEN placebo-controlled trials<sup>6</sup>
  - Indirect comparison, 10 studies included (6 D, 4 V); N=1754 pts
  - Primary outcome of remission and response (HAM-D)
  - Remission VEN 17.8% (9-26.5) and DUL 14.2% (8.9-26.5) >PBO

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## Clinical trials...

- Relapse prevention<sup>7</sup>
  - Industry sponsored
  - Treated 533 pts for 12 wks on duloxetine 60 mg/d -- the pts who responded (52%) went on to be randomized to PBO or DUL for 26 wks
  - Relapse rates DUL 17.4% vs PBO 28.5% (ss)
    - ARR 11 % NNT 9 for 26 wks to prevent 1 relapse

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## Summary

- Approximately 50-70% pts with major depression respond to an initial antidepressant; only 30-40% achieve full remission
  - Current guidelines therapy of depression suggests use of SSRI or SNRI (Venlafaxine) as first-line therapy
    - Some debate on whether venlafaxine is superior to SSRI's
- Duloxetine
  - Superior to placebo. Possibly inferior to escitalopram and venlafaxine.
  - No other true head-to-head data ... need more studies before considering it a first line agent
  - Consideration for pts with depression and pain

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## Questions??

Thank-you!!

Have YOU considered volunteering for CSHP ??  
Talk to a council member today!!!