

# Antipsychotic Treatment and Withdrawal for Behavioural and Psychological Symptoms of Dementia

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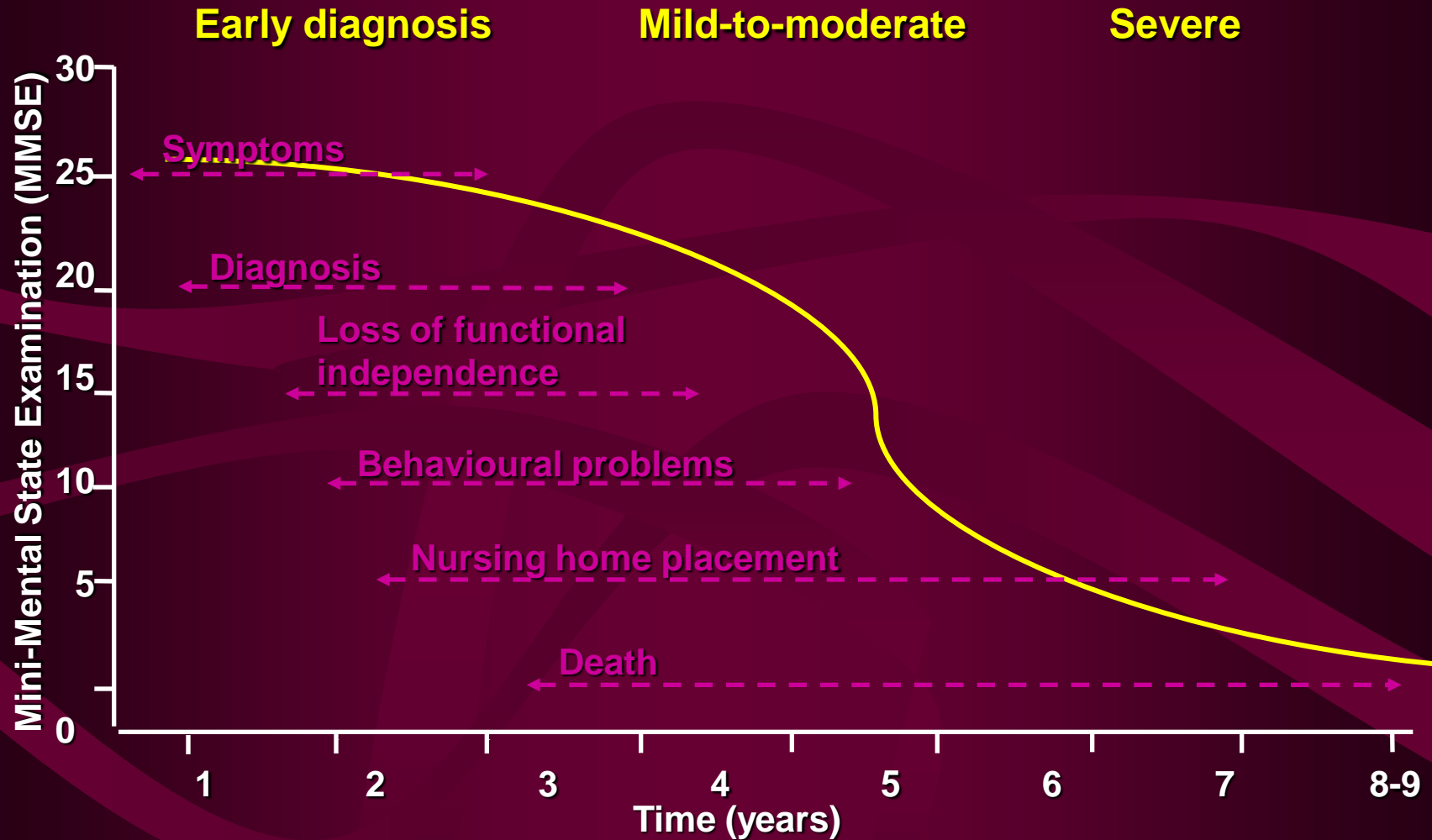
# Learning Objectives

- Understand the guidelines surrounding treating BPSD and withdrawing treatment
- Understand the benefits and risks of atypical antipsychotics in treating BPSD

# Disclosure for Dr. Chan

- Speaker honourarium from:
  - Astra-Zeneca
  - Eli-Lilly
  - Janssen-Ortho
  - Lundbeck
  - Organon

# Natural History of AD



*Reproduced from Feldman and Gracon, 1996.*

# Behavioral and Psychological Symptoms of Dementia

- Present in 50% of outpatients and 75% of nursing home patients with Alzheimer's disease
- Symptoms include
  - Agitation/Aggression
  - Hostility
  - Psychosis
  - Insomnia
  - Withdrawal
  - Depression
  - Anxiety
  - Wandering
  - Repetitive vocalizations

# Pharmacotherapy for BPSD

- Typical Antipsychotics
- Atypical Antipsychotics
- Antidepressants
- Mood Stabilizers
- Cholinesterase inhibitors
- Memantine

# Atypical Antipsychotics in Cochrane Review (Ballard 2006): Beneficial effects

- Risperidone and olanzapine have similar efficacy in aggression
- Risperidone also efficacious in psychosis
- High placebo response rates: up to 40%
- Quetiapine: only 1 analyzed—no effect
- Dosage range
  - Risperidone 0.5 – 2 mg/d
  - Olanzapine 2.5 – 15 mg/d
  - Quetiapine 25 – 200 mg/d
- Many studies enrolled severely demented, institutionalized patients

# Review of RCT's of BPSD's and Atypical Antipsychotics

- Risperidone: 5 studies (3 placebo, 2 haldol)
- Olanzapine: 3 studies (placebo)
- Quetiapine: 2 studies (placebo, comparator)
- Aripiprazole: 1 study (placebo).
- Placebo improvement rates: 5-37%
- Medication advantage over placebo: 8-25%
- Some showed no sig diff in psychosis, CGI.

Bannerjee, S. The use of antipsychotic medication for people with dementia: Time for action. Report to UK Dept of Health, 2009  
[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_108302.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_108302.pdf)

- “Effect sizes for most atypical antipsychotic drugs on the outcome measures that assess global behavioural disturbance are in the range of 0.1 to 0.2, which is very low.”

# Quetiapine IR and BPSD

| Study                                   | Medication  | Patient Group   | Efficacy  | Adverse Effects   |
|---|---|---|---|---|
| Kurlan et al. Neurology 2007            | Quetiapine:<br>Aim for 100 mg/d<br>Mean dose=120 mg/d<br><br>Placebo<br>(Majority on AchEI's)   | 40 patients<br>Lewy Body,<br>PD with dementia,<br>AD with Parkin.<br>(Moderate severity)<br><br>10 week trial | BPRS, NPI,<br>CGI:<br><br>No sig. Diff.                                 | Lightheadedness<br>but no dropouts.<br><br>No cognitive or<br>Parkinsonian<br>worsening |
| Zhong et al. Curr. Alz. Res. 2007       | Quetiapine 200 mg/d<br>(by Day 8). Fixed<br>Quetiapine 100 mg/d<br>(by Day 4). Fixed<br>Placebo | 333 facility care<br>patients with<br>severe Dementia<br><br>10 week trial                                    | 200 mg/d over<br>placebo, not<br>100 mg/d<br>Post-hoc<br>analysis CGI   | Q: 10% lethargy<br>and somnolence,<br>5% gait change, 3%<br>postural<br>hypotension.    |
| Paleacu et al. Int. J. Geri. Psyc. 2008 | Quetiapine:<br>Aim for 150 mg/d<br>Max 300 mg/d<br><br>Placebo                                  | 40 patients with<br>moderate dementia<br><br>6 week trial   | NPI, CGI:<br>No sig. Diff.<br><br>200-300 mg/d<br>group better          | No sig diff between<br>groups. No<br>cognitive or<br>Parkinsonian<br>worsening          |
| Tariot et al. Am. J. Geri Psyc 2006     | Quetiapine:<br>(Mean 96.9 mg/d)<br>Haloperidol<br>(Mean 1.9 mg/d)<br>Placebo                    | 284 facility care<br>patients with<br>MMSE avg 13<br><br>10 week trial  | Agitation<br>improved in<br>med group.<br>Psychosis<br>improved in all. | 25-36%<br>somnolence in Q<br>and H. Groups.<br>Haldol had most<br>EPS.                  |

# Aripiprazole and BPSD

| Study   | Medications   | Patient Group  | Efficacy   | Adverse Effects   |
|---|---|--|--|---|
| De Deyn et al.<br>J. Clin.<br>Psychopharm.<br><u>2005</u> | ARI, 5–15 mg/d<br><br>Mean dose=10 mg/d                 | 208 outpatients<br><br>10 weeks                            | NPI Psychosis:<br><b>ARI = PLA</b><br><br>BPRS, CGI-S:<br>ARI > PLA  | Somnolence:<br><br>ARI: 8%<br>PLA: 5%<br><br>No sig EPS diff.   |
| Streim et al.<br>Am J. Geri Psych.<br><u>2008</u>         | ARI, 2–15 mg/d<br><br>Placebo                           | 266 patients<br><br>Nursing home residents<br><br>10 weeks | NPI Psychosis:<br><b>ARI = PLA</b><br><br>BPRS, CGI-S,<br>CMAI:<br>ARI > PLA   | Somnolence:<br><br>ARI: 14%<br>PLA: 4%<br><br>No sig. EPS diff.   |
| Mintzer et al.<br>Am. J. Geri.<br>Psych. <u>2007</u>      | ARI(fixed):<br><br>2, 5, 10 mg/d<br><br>Placebo (n=112) | 487 patients<br><br>Nursing home residents<br><br>10 weeks | NPI Psychosis<br>(10 mg dose):<br><b>ARI &gt; PLA</b><br><br>BPRS, CGI-I,<br>CGI-S, CMAI:<br>ARI > PLA<br>(5 , 10 mg dose) | 7 CVAE's in ARI group, none in PLA group (Same mortality risk)<br><br>Somnolence: 2-3X<br><br>No sig. EPS diff. |

# Atypical Antipsychotics in Cochrane Review (Ballard 2006): Adverse Effects

- Somnolence
- EPS
- Falls
- Abnormal gait
- Urinary incontinence
- URTI: risp
- UTI: risp
- Peripheral edema: risp

# Warnings, Warnings, Warnings

- **Avoid antipsychotic drugs for elderly, experts urge, after death risk study**

Doctors should try not to prescribe antipsychotic drugs for elderly people with Alzheimer's, geriatricians said following new research that concluded taking people taking the medications had double the risk of dying during the course of the study.

(09/01/2009 11:51:42 AM CBC News)

- **Antipsychotic drugs raise risks for dementia patients**

Elderly patients with dementia who are put on antipsychotic medication are more likely to be hospitalized or die within 30 days of first using the drug than those who are not put on the drugs, a new Canadian study says.

(May. 26 2008 5:53 PM ET CTV.ca News )

# Atypical Antipsychotics: Catastrophic Adverse Effects

- Mortality risk
  - OR 1.7 times (FDA April 2005)
    - 17 studies, 5106 pts, 4.5% vs 2.6% placebo
  - OR 1.54 times (Schneider JAMA 2005;294:15)
    - 15 studies, 3353 pts, 3.5% vs 2.3% placebo
- CVA effects (Brodaty 2005; Kryszhanovskaya 2006)
  - 3-4 times risk
  - Risp: 6 RCT's, 1721 pts, 3.3% vs 1.1% placebo
  - Olanz: 5 RCT's, 1656 pts., 1.3% vs. 0.4% placebo

Bannerjee, S. The use of antipsychotic medication for people with dementia: Time for action. Report to UK Dept of Health, 2009

- “15 randomised placebo-controlled trials of atypical antipsychotics provides robust evidence for an increased risk of CVAEs, with a pooled relative risk of 2.57 (95% CI 1.41-4.66)”

# Serious Adverse Effects: Typical vs. Atypical AP's

## – Douglas et al. BMJ 2008; 337:a1227

- 6790 UK GP Research Database
- Use of any antipsychotic drug and stroke ratio risk: 1.73
  - 1.69 for typical antipsychotics and 2.32 for atypical antipsychotics.
- In patients receiving any antipsychotic drug, the rate ratios were
  - 3.50 (2.97 to 4.12) with dementia and 1.41 (1.29 to 1.55) without.

## – Wang et al. NEJM 2005; 353:22

- 22890 Penn. Pharmacare database pts, 1994-2003
- Risk of death within 180 days
- Higher relative risk of Mortality: 1.37 in typical grp. Higher risk in higher dose group, indep. Of dementia and LTC.

## – Hollis et al. Am J. Geri Psych 2008; 15:11

- 16634 users Veteran pharm. database 2003-04
- 2 yr follow-up., risk of death
- Haloperidol highest risk: 2.26 compared to Olanzapine
- Compared other AP's, carbamazepine, valproic acid

# When starting an Atypical...

- Documented rationale (LTC practice guidelines)?
  - Severe distress
  - Harm to self or others
  - Harm to caregivers
- Short-term or longer-term use, contraindications?
  - Delirium
  - Evolving CVA or previous major CVA's, Diuretic (Lasix)
- Discussion and documentation of discussion with patient or substitute decision-maker?
- Considered other options?
  - Non-pharmacologic vs. Other pharmacologic treatments
- Sensitivity to AP's?
  - Lewy Body Dementia, Parkinson's Disease with Dementia

# Weighing Risk vs. Benefits of atypicals

- NNT for benefit: 5 - 14 patients
- NNH for mortality: 100 patients
- 1 patient death for every 9 – 25 who benefit

# Benefits vs. Risks

Bannerjee, S. The use of antipsychotic medication for people with dementia: Time for action. Report to UK Dept of Health, 2009

“..treating 1,000 people with BPSD with an atypical antipsychotic drug for around 12 weeks would result in..

- an additional 91–200 patients with behaviour disturbance (or an additional 72 patients of 1,000 with psychosis) showing clinically significant improvement in these symptoms;
- an additional 10 deaths;
- an additional 18 CVAEs, around half of which may be severe;
- no additional falls or fractures; and
- an additional 58–94 patients with gait disturbance.”

# Atypical Antipsychotics Effectiveness:

## CATIE-AD

Schneider et al. NEJM 2006

- RCT, 421 AD pts; MMSE mean = 15; 36 wks trial
- Indep living or assisted living facility, caregiver available
- Use of other psychotropics allowed
- Randomized
  - Olanzapine mean dose= 5.5 mg/d
  - Quetiapine mean dose= 56.6 mg/d
  - Risperidone mean dose= 1.0 mg/d
  - Placebo

**Conclusion:** No sig diff in groups; higher drop out rates in drug group due to intolerability. Adverse effects offset advantages

# DART-AD Trial

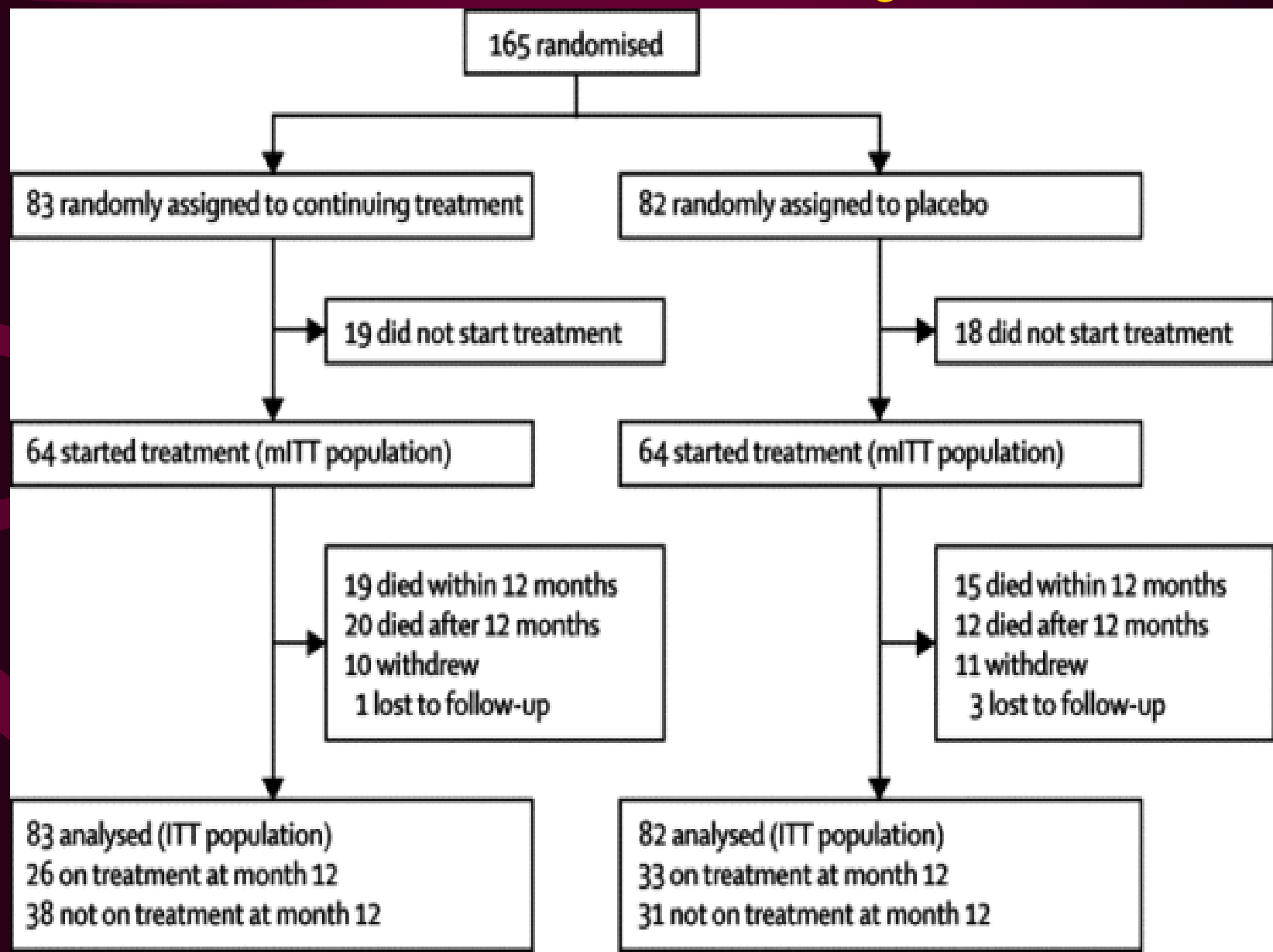
Ballard et al. Plos Medicine 2008; Lancet Neurology January 9, 2009

- n=165 residential care, AD, mean MMSE=11
- Placebo vs AP's continuation over 12 months
- Cumulative probability of survival during the 12 months was 70% (95% CI 58–80%) in the continue treatment group versus 77% (64–85%) in the placebo group (mITT population= 128)
- 24-month survival 46% vs 71%; 36-month survival 30% vs 59% (telephone assessment and death certificate review)
- 50-60% died or dropped out by 12 months

# DART-AD Trial: Demographics

|   | Continue treatment (n=83)        | Placebo (n=82)                   |
|---|----------------------------------|----------------------------------|
| Women (%)                                 | 64 (77%)                         | 62 (76%)                         |
| Age (mean and s.d. years)                 | 84.8 (7.0)<br>range=68.3–100.2   | 84.9 (6.1)<br>range=67.0–100.6   |
| Sig. EPS (%)                              | 39 (47%)                         | 39 (48%)                         |
| Visual hallucinations                     | 10 (12%)                         | 10 (12%)                         |
| Delusional                                | 27 (33%)                         | 27 (33%)                         |
| Cholinesterase inhibitor                  | 2 (2%)                           | 3 (4%)                           |
| Atypical neuroleptic before randomisation | 57 (69%)                         | 58 (71%)                         |
| SMMSE (SD);                               | 11 (6) [n=83]                    | 11 (5) [n=82]                    |
| SIB Mean (SD);<br>Median (range)          | 71.1 (22.7) [n=75]<br>77 (58–91) | 73.8 (20.7) [n=71]<br>80 (63–92) |
| NPI Mean (SD);<br>Median (range)          | 17.4 (14.6) [n=75]<br>15 (5–24)  | 15.8 (11.3) [n=70]<br>14 (6–24)  |

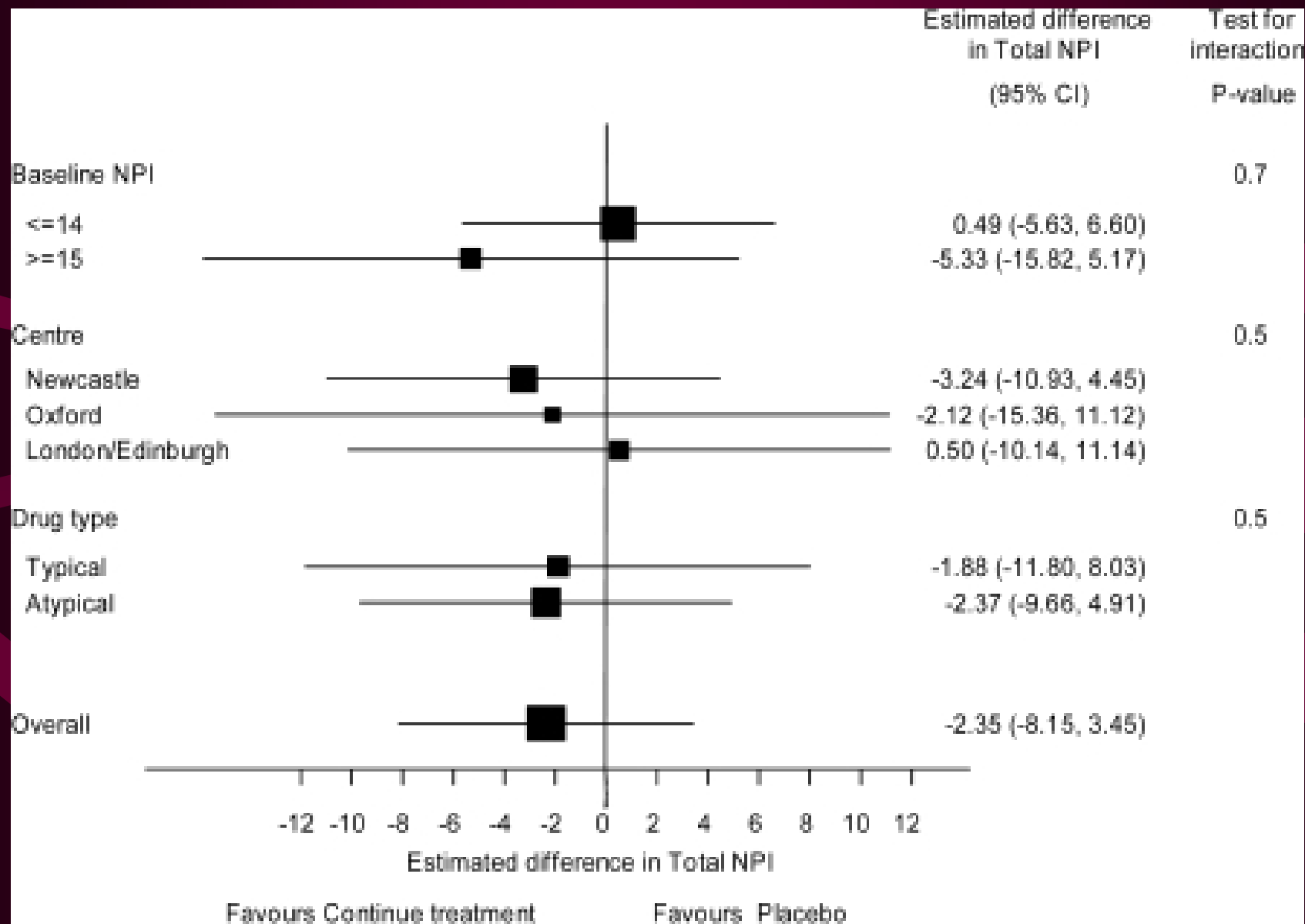
# DART-AD Trial: Subject Flow



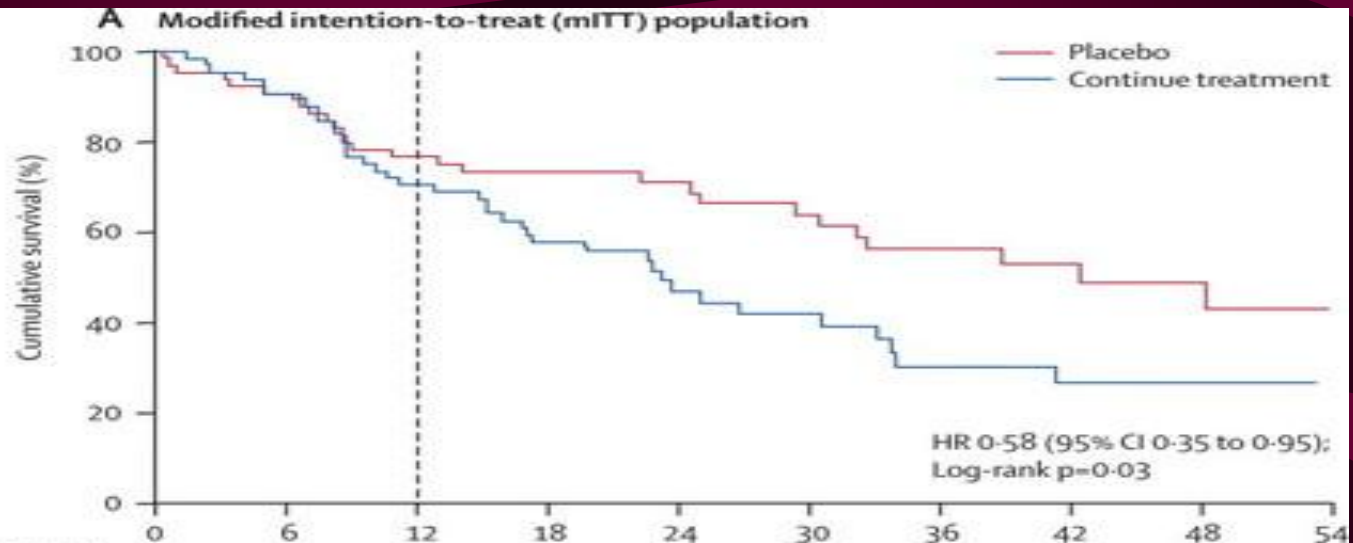
# DART-AD: Antipsychotic Dosing

| Neuroleptic     | Very Low           | Low                 | High               |
|-----------------|--------------------|---------------------|--------------------|
| Risperidone     | 0.5 mg once daily  | 0.5 mg twice daily  | 1 mg twice daily   |
| Chlorpromazine  | 12.5 mg once daily | 12.5 mg twice daily | 25 mg twice daily  |
| Trifluoperazine | 0.5 mg once daily  | 0.5 mg twice daily  | 1 mg twice daily   |
| Haloperidol     | 0.75 mg once daily | 0.75 mg twice daily | 1.5 mg twice daily |

# DART-AD Trial: NPI Results

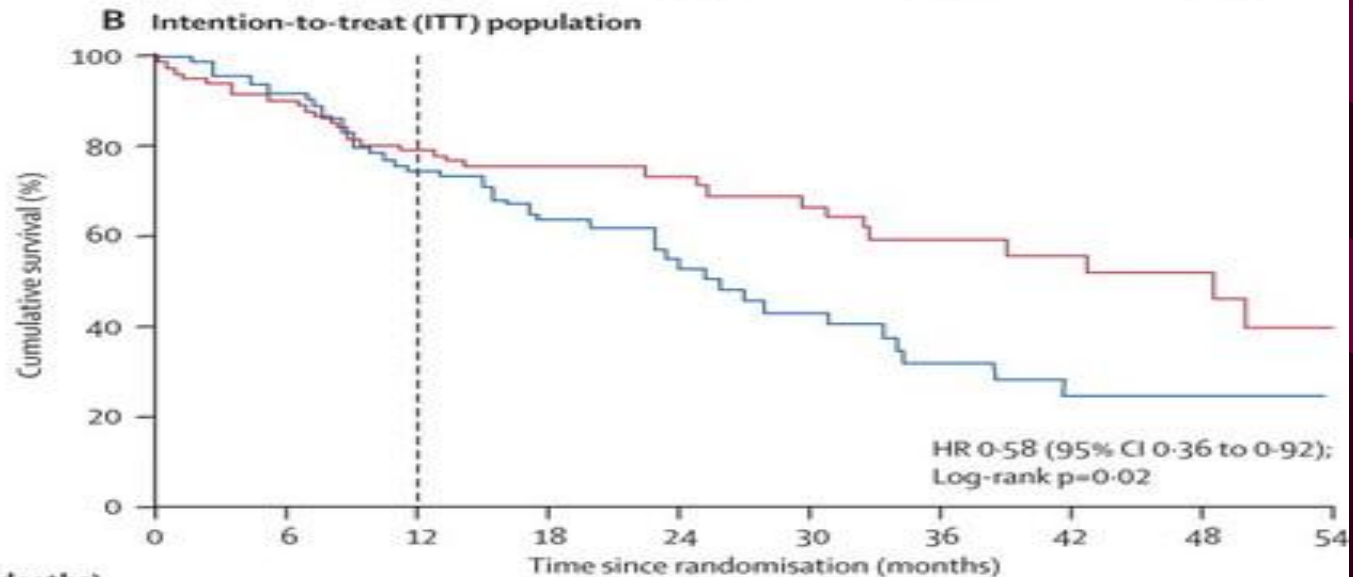


# DART-AD Trial: Survival



Number at risk (deaths)

|                    |         |         |        |        |       |
|--------------------|---------|---------|--------|--------|-------|
| Continue treatment | 64 (19) | 45 (13) | 20 (6) | 9 (1)  | 4 (0) |
| Placebo            | 64 (15) | 49 (3)  | 29 (6) | 19 (2) | 8 (1) |



Number at risk (deaths)

|                    |         |         |        |        |       |
|--------------------|---------|---------|--------|--------|-------|
| Continue treatment | 83 (21) | 62 (14) | 23 (8) | 10 (2) | 4 (0) |
| Placebo            | 82 (17) | 65 (4)  | 32 (6) | 21 (2) | 9 (2) |

# Conclusions from the DART-AD Trial

- Treatment with neuroleptics was NOT associated with significantly greater decline in global cognition (SIB)
- Sig. deterioration in verbal fluency for patients taking neuroleptics
- Withdrawal of neuroleptics had no overall detrimental effect on functional and cognitive status
- “Severe” BPSD with NPI >14: there were modest benefits at 6 mo and more substantial advantages at 12 mo in those on AP’s, not placebo.
- Increase in mortality at 12 months in the patients who continued antipsychotic treatment (5–8% greater than placebo)
- Higher rate of mortality in the patients who were randomized to continue antipsychotic medication compared with those who were randomised to discontinue antipsychotic medication particularly at 24, 36, and 48 months.
- No evidence of excessively increased mortality due to cerebrovascular causes in the patients assigned to antipsychotic treatment.

# Analysis of the DART-AD Trial

- High dropout rates limit interpretation
- NPI score  $> 14$  not necessarily “severe” BPSD
- Subscales of NPI scores not published, so AP’s may have differential effects on BPSD
- Conclusion there is an increased mortality with AP’s over placebo at 12 months despite overlapping confidence intervals and despite analysis on the mITT, ITT, and completer groups at 12 months
- Kaplan-Meier analysis based on survival up to 54 months, despite randomized control portion being terminated 12 months. Lack of clarity how much the each subject kept to its assigned treatment
- Generalizability of results: severe Dementia subject population
- Substantial number of individuals had sig. EPS to start with, and no mention as to how that affected outcome, incl. EPS and mortality risk
- BIAS, BIAS, BIAS!

# Ballard...

- “Some of the changes in NPI score are likely to be related to natural symptom course, or a Hawthorne effect, or regression to the mean, although there should be no imbalance in these factors between groups.”

# Ballard..

- “One possible explanation for our findings is that the most frail participants who had the most severe dementia (ie, those most likely to die within 12 months) have a high mortality risk regardless of whichever treatment is assigned. Another possible explanation is that the close monitoring afforded during a clinical trial was able to mitigate the effect of important adverse outcomes.”

# VCH Regional Practice Guidelines: ATYPICAL Antipsychotic Treatment for BPSD

- Developed for: All VCH-PHC Acute and Residential Sites
- Developed by:
  - Dr Peter Chan, Psychiatrist VA and Residential
  - Dr Liz Drance, Medical Director, VC Mental Health, Older Adult Mental Health
  - Dr Mike Passmore, Psychiatrist MSJ
  - Dr Jane de Lemos, PharmD, Regional Coordinator, Professional Practice, VCH-PHC Pharmacy
  - Dr Cait O’Sullivan (**Lead**) PharmD Clinical Pharmacist, Powell River
- Endorsed by:
  - Regional Pharmacy and Therapeutics Committee March 22nd 2010
- Start with an appropriately low dose: Consider risperidone 0.25 mg/d, olanzapine 2.5 mg/d, quetiapine 12.5-25 mg/d as suggested starting doses.
- Make a decision regarding effectiveness by 8 weeks.
- Review for drug taper after a 3 to 6 month period of behavioural stability.
- Individualize treatment duration taking into account: patient’s functional status, target symptom, duration/persistence/severity of symptoms.

# Conclusions: Medications and BPSD

- More “severe” BPSD, especially aggression, may be especially amenable to treatment with AP’s
- Conflicting literature on how effective AP’s are for psychosis
- Alternative pharmacotherapies should be considered, especially when less severe symptoms
- Safety and tolerability need to be weighed against benefit when using AP’s; there is no good evidence beyond 3 months for increased mortality or CV Ae.
- Withdrawing of medications should be done cautiously after 3-6 months of stability