

# Discontinuing Antipsychotics in Dementia: What is the Evidence?

Dr Bradley Ng

OPMH, Gold Coast

Bond and Auckland Universities

# Declarations

---

- No conflicts of interest to declare
- Thanks
  - ▣ Inpatient and outpatient teams
  - ▣ University of Auckland library service

# Antipsychotics in Dementia

- Used to treat biological and psychological symptoms of dementia
  - Agitation
  - Verbal aggression
  - Physical aggression
  - Irritability
  - Psychotic symptoms
  - Depression
  - Anxiety

# Which ones do we use?

- Risperidone
- Haloperidol
- Olanzapine
- Quetiapine
- Aripiprazole

# What we think we know?

- Do they work? Not really
- Is there evidence for them? Modest
- Do they cause problems? Definitely
- Are they over-prescribed? Yes
- Are the doses too big? Yes
- Do people stay on them too long? Yes

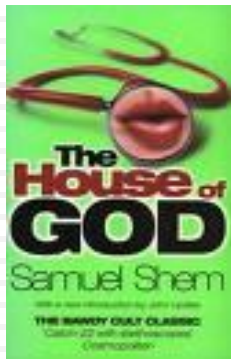
# So why are they prescribed?

- Don't just do something, stand there!
- Acuity
- Pressure from other interested parties
- Non-pharmacological methods take too long
- Non-pharmacological methods are not available
- Risk to one versus the risk to others

The art of medicine is to do as much  
nothing as possible

House of God

Samuel Shem



# Old Age Psychiatry and Medication

- Stop something
- Stop lots of things
- Stop everything
- Reduce the dose
- Change the timing
- Change the medicine
- Increase the dose
- Add a new medication

# Discontinuing Antipsychotics

- ❑ The antipsychotic may not be helpful
- ❑ BPSD fluctuate
- ❑ The environment has changed
- ❑ Another intervention has been done
- ❑ There might be something safer
- ❑ Minimising unnecessary medications
- ❑ Minimising drug side effects
- ❑ Minimising potential medication interactions
- ❑ Optimising physical health
- ❑ Optimising cognition



# SO IS THERE ANY EVIDENCE FOR BENEFIT WHEN DISCONTINUING ANTIPSYCHOTICS?

Quite a lot actually! There are a number of medication withdrawal trials.

# FINDLAY et al (1989)

- Thirty six women with Alzheimer's Dementia
- Long stay wards
- 10-100mg thioridazine (mode 20mg)
- On medication for at least 2 months
- Double blind randomised withdrawal trial
- Placebo versus drug (usual medication)
- Medication halved for week one then ceased

# FINDLAY et al (1989)

- Measurements baseline, week 2, week 4
- No differences between the two groups
  - ▣ Cognitive function
  - ▣ Behaviour
  - ▣ Physical state
- No evidence of withdrawal phenomenon
- 17/18 patients in both groups completed trial

# FINDLAY et al (1989)

- One patient in each group required regular replacement medication (chlormethiazole)
- Two in placebo group and one in drug group required replacement medication once
- Modest doses of thioridazine may be withdrawn without major short-term physical or psychiatric deterioration

# BRIDGES-PARLAT et al (1997)

- 36 patients with dementia
- Documented physical aggression
- Five dementia units referred patients
- On FGA for at least 3 months
- Double blind randomised withdrawal trial
- Placebo (22) versus drug (14) treatment
- Medication tapered or suddenly ceased

# BRIDGES-PARLAT et al (1997)

- Measurements week 0 (baseline), 2, 4
- Primary endpoint was completion of trial participation
- Direct observation of physical aggression acts
  - ▣ Two hour periods, four times per week
  - ▣ Researcher coded
- Two groups similar
  - ▣ Early 80s, female 80%, one had MMSE >4
  - ▣ Over two thirds of placebo group physically aggressive in baseline week

# BRIDGES-PARLAT et al (1997)

- Trial completion similar (NS)
  - ▣ Placebo patients 91% (20/22)
  - ▣ Drug patients 100% (14/14)
- One patient restarted on thioridazine and one patient treated with clonazepam.
- No difference in
  - ▣ Observed physical aggression
  - ▣ Proportions of clinical changes in individual subjects
- After trial 11/20 placebo patients remained off antipsychotics (mean 40 weeks; range 1-156)

# BRIDGES-PARLAT et al (1997)

- Selected population- was there a belief that discontinuing medications could work?
- But sample was quite severe.
- Observation that medication was restarted for agitation or intrusiveness rather than aggression.
- Withdrawing medications did not lead to a dramatic deterioration in most patients
- Concluded that physical aggression, or history of it, should not drive continuing antipsychotic use

# COHEN-MANSFIELD et al (1999)

- 58 patients (43 women; average age 86)
- Older than 70 years
- No major affective disorder or schizophrenia
- 550 bed facility
- Lots of exclusions!
- Haloperidol, thioridazine, lorazepam >4 weeks
- Double blind cross over randomised withdrawal trial
- Taper and either “placebo” or “drug” periods

# COHEN-MANSFIELD et al (1999)

## □ Measurements

- 2<sup>nd</sup> week baseline
- 1 week after taper and 6 weeks after “full withdrawal”
- 1 week after 2<sup>nd</sup> taper and 6 weeks after 2<sup>nd</sup> “full withdrawal”

## □ Primary measures

- BPRS
- CMAI

# COHEN-MANSFIELD et al (1999)

- 23 Discontinuations, 20 in 1<sup>st</sup> stage
  - 12 on drug
  - 9 on placebo
  - 2 while titrating from drug to placebo
- 9/23 Discontinuations due to agitation
  - 6 on drug
  - 3 on placebo
- No difference between discontinuers and completers
  - Dose
  - BPRS
  - CMAI

# COHEN-MANSFIELD et al (1999)

- No changes in scores
- Withdrawal did not led to improved functioning
- When behaviour worsened staff thought it was due to placebo
- Blinding broken- no differences
- Staff fears and perceptions about medication

# VAN REEKUM et al (2002)

- 34 patients with any dementia
- Two facilities and an academic centre
- On stable antipsychotic for at least 3 months
- Excluded if previous withdrawal failure
- BEHAVE-AD <3 on Behavioural Pathology
- Double blind randomised withdrawal trial
- Placebo (17) versus drug (16) treatment
- 2 week baseline, 2 week dose reduction
- 26 week trial with 15 visits

# VAN REEKUM et al (2002)

- Prn lorazepam only
- Discontinued if
  - ▣ BEHAVE-AD 3 or more
  - ▣ Clinical staff noted significant worsening
- No differences between groups
  - ▣ Early 80s, MMSE 6-8, NPI 12-17
- Discontinuation all reasons
  - ▣ 10 (58.8%) placebo versus
  - ▣ 6 drug (37.5%) [RR: 1.57, 0.76-3.26]

# VAN REEKUM et al (2002)

- Discontinuation due to “behavioural problems”
  - ▣ 4 (23.5%) placebo versus
  - ▣ 3 (18.8%) drug
- Larger doses predicted discontinuation due to behaviour in total and placebo groups
- Most ratings unchanged
- Concluded that discontinuation of antipsychotics does not lead to deterioration
- High doses of antipsychotics should be tapered and clinical states monitored.

# RUTHS et al (2004)- Bergen District Nursing Study

- 30 patients with dementia
- Dementia and over 65 years of age
- Nine institutions referred patients
- Resident for at least three months
- On stable antipsychotic for at least 3 months
- Double blind randomised withdrawal trial
- Placebo (15) versus drug (15) treatment

# RUTHS et al (2004)

- Medication suddenly ceased at end of two week baseline period
- Measurements 2<sup>nd</sup> baseline week, week 2 & 4
- Neuropsychiatric Inventory Questionnaire (NPI-Q) (score 0-36)
- Actigraphy for sleep/wake activity
- Treating doctor allowed to “restart” antipsychotic



Study Name or Acronym: \_\_\_\_\_

**NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)**

9 6

4 0

SUBJECT ID

VISIT NO

DATA SOURCE

SITE NO

VISIT DATE

MM

DD

YYYY

Please ask the following questions based upon changes.

Indicate "yes" only if the symptom has been present in the past month; otherwise, indicate "no".

Rate the **DISTRESS** you (the caregiver) experience because of the symptom (how it affects you):

- 0 = Not distressing at all
- 1 = Minimal (slightly distressing, not a problem to cope with)
- 2 = Mild (not very distressing, generally easy to cope with)
- 3 = Moderate (fairly distressing, not always easy to cope with)
- 4 = Severe (very distressing, difficult to cope with)
- 5 = Extreme or very severe (extremely distressing, unable to cope with)

Rate the **SEVERITY** of the symptom

- (how it affects the patient):
- 1 = Mild (noticeable, but not a significant change)
  - 2 = Moderate (significant, but not a dramatic change)
  - 3 = Severe (very marked or prominent; a dramatic change)

Present in the PAST MONTH:  
0 = No  
1 = Yes

**DELUSIONS**

- |   |     |                      |     |                      |     |                      |
|---|-----|----------------------|-----|----------------------|-----|----------------------|
| 1. Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way? | 1.1 | <input type="text"/> | 1.2 | <input type="text"/> | 1.3 | <input type="text"/> |
|---|-----|----------------------|-----|----------------------|-----|----------------------|

**HALLUCINATIONS**

- |   |     |                      |     |                      |     |                      |
|---|-----|----------------------|-----|----------------------|-----|----------------------|
| 2. Does the patient act as if he or she hears voices?<br>Does he or she talk to people who are not there? | 2.1 | <input type="text"/> | 2.2 | <input type="text"/> | 2.3 | <input type="text"/> |
|---|-----|----------------------|-----|----------------------|-----|----------------------|

**AGITATION OR AGGRESSION**

- |   |     |                      |     |                      |     |                      |
|---|-----|----------------------|-----|----------------------|-----|----------------------|
| 3. Is the patient stubborn and resistive to help from others? | 3.1 | <input type="text"/> | 3.2 | <input type="text"/> | 3.3 | <input type="text"/> |
|---|-----|----------------------|-----|----------------------|-----|----------------------|

**DEPRESSION OR DYSPHORIA**

- |   |     |                      |     |                      |     |                      |
|---|-----|----------------------|-----|----------------------|-----|----------------------|
| 4. Does the patient act as if he or she is sad or in low spirits? Does he or she cry? | 4.1 | <input type="text"/> | 4.2 | <input type="text"/> | 4.3 | <input type="text"/> |
|---|-----|----------------------|-----|----------------------|-----|----------------------|

**ANXIETY**

- |  |     |                      |     |                      |     |                      |
|--|-----|----------------------|-----|----------------------|-----|----------------------|
| 5. Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense? | 5.1 | <input type="text"/> | 5.2 | <input type="text"/> | 5.3 | <input type="text"/> |
|--|-----|----------------------|-----|----------------------|-----|----------------------|

**ELATION OR EUPHORIA**

- |   |     |                      |     |                      |     |                      |
|---|-----|----------------------|-----|----------------------|-----|----------------------|
| 6. Does the patient appear to feel too good or act excessively happy? | 6.1 | <input type="text"/> | 6.2 | <input type="text"/> | 6.3 | <input type="text"/> |
|---|-----|----------------------|-----|----------------------|-----|----------------------|

**APATHY OR INDIFFERENCE**

- |  |     |                      |     |                      |     |                      |
|--|-----|----------------------|-----|----------------------|-----|----------------------|
| 7. Does the patient seem less interested in his or her usual activities and in the activities and plans of others? | 7.1 | <input type="text"/> | 7.2 | <input type="text"/> | 7.3 | <input type="text"/> |
|--|-----|----------------------|-----|----------------------|-----|----------------------|

# RUTHS et al (2004)

- Two groups similar at baseline
  - ▣ 24 women, mean age 83.4, resident 30 months
  - ▣ Medication average 14 months
  - ▣ Risperidone 0.5mg, olanzapine 5mg, haloperidol 0.75mg
  - ▣ Most commonly prescribed for agitation, aggression and restlessness
- NPI-Q between placebo and active group
  - ▣ Total scores not significantly different
  - ▣ Only significant difference in restlessness change

# RUTHS et al (2004)

- In placebo group
  - ▣ NPI-Q sum scores stable or decreased in 11
  - ▣ Increased in 4 patients (aggression/agitation)
- Only one patient in the placebo group had medication restarted
- Confirmed conclusions of previous studies

# RUTHS et al (2008)

- Extension of 2004 study
- 55 patients with dementia
- Same inclusion criteria
- Thirteen institutions referred patients
- Double blind randomised withdrawal trial
- Placebo (27) versus drug (28) treatment
- Medication suddenly ceased at end of two week baseline period

# RUTHS et al (2008)

- Primary outcome study completion
- Treating doctor allowed to “restart” antipsychotic
- Measurements 2<sup>nd</sup> baseline week, week 2 & 4
- Neuropsychiatric Inventory Questionnaire (NPI-Q)  
(score 0-36)

# RUTHS et al (2008)

- Two groups similar at baseline
  - ▣ 43 women, mean age 84.1, resident 33 months
  - ▣ Medication average 17 months
  - ▣ Risperidone 1.0mg, olanzapine 5mg, haloperidol 1.0 mg
- Completers 23/27 placebo 25/28 drug group
- Two in placebo group discontinued due to agitation and 0 in the drug group (NS)
- NPI-Q between placebo and active group no different (total, individual, factors)

# RUTHS et al (2008)

- In the placebo group
  - ▣ 11/24 (46%) and 8/24 (33%) remained off drug after 1 and 3 months respectively
  - ▣ trend for patients with higher NPI scores to be restarted on drug
- In the drug group
  - ▣ 10/28 (36%) and 6/27 (22%) were off drug 1 and 3 months respectively
- Recommend trials of drug cessation be taken at regular intervals

# BALLARD et al (2004)

- 100 patients over 65yo with Alzheimer's Dementia
- Facilities in Newcastle and Oxford
- Criteria for diagnosis and severity
- No individual NPI score  $>7$
- On stable antipsychotic for at least 3 months
- Double blind randomised withdrawal trial
- Placebo (46) versus drug (54) treatment
- No tapering



Study Name or Acronym: \_\_\_\_\_  
**NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)**

9 6

4 0

SUBJECT ID

VISIT NO

DATA SOURCE

SITE NO

VISIT DATE

MM

DD

YYYY

Please ask the following questions based upon changes.

Indicate "yes" only if the symptom has been present in the past month; otherwise, indicate "no".

Rate the **DISTRESS** you (the caregiver) experience because of the symptom (how it affects you):

- 0 = Not distressing at all
- 1 = Minimal (slightly distressing, not a problem to cope with)
- 2 = Mild (not very distressing, generally easy to cope with)
- 3 = Moderate (fairly distressing, not always easy to cope with)
- 4 = Severe (very distressing, difficult to cope with)
- 5 = Extreme or very severe (extremely distressing, unable to cope with)

Rate the **SEVERITY** of the symptom (how it affects the patient):

- 1 = Mild (noticeable, but not a significant change)
- 2 = Moderate (significant, but not a dramatic change)
- 3 = Severe (very marked or prominent; a dramatic change)

Present in the **PAST MONTH**:  
 0 = No  
 1 = Yes

**DELUSIONS**

1. Does the patient believe that others are stealing from him or her, or planning to harm him or her in some way?

1.1

1.2

1.3

**HALLUCINATIONS**

2. Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?

2.1

2.2

2.3

**AGITATION OR AGGRESSION**

3. Is the patient stubborn and resistive to help from others?

3.1

3.2

3.3

**DEPRESSION OR DYSPHORIA**

4. Does the patient act as if he or she is sad or in low spirits? Does he or she cry?

4.1

4.2

4.3

**ANXIETY**

5. Does the patient become upset when separated from you? Does he or she have any other signs of nervousness, such as shortness of breath, sighing, being unable to relax, or feeling excessively tense?

5.1

5.2

5.3

**ELATION OR EUPHORIA**

6. Does the patient appear to feel too good or act excessively happy?

6.1

6.2

6.3

**APATHY OR INDIFFERENCE**

7. Does the patient seem less interested in his or her usual activities and in the activities and plans of others?

7.1

7.2

7.3

# Ballard (2004)

- Baseline, 1 month, 3 month
- NPI and DCM
- Proportion of trial discontinuations
- Two groups similar at baseline
  - 81 women, early to mid 80s
  - Median MMSE 3; NPI scores 14-16

# Ballard (2004)

- Discontinuations 14/46 (30%) and 14/54 (26%) all reasons (NS)
- Discontinuations 6/46 (13%) and 5/54 (9%) due to behavioural deterioration (NS)
- 36 placebo and 46 drug completed 1 month of follow up and no changes on NPI
  - Total scores
  - Factors scores of agitation, mood and psychosis

# Ballard (2004)

- In patients with  $NPI > 14$ 
  - ▣ On drug less likely to develop marked behavioral disturbance compared to placebo
  - ▣ On placebo more likely to have marked behavioural disturbance compared to  $NPI < 14$
  - ▣ But no significant differences in NPI total scores or factor scores
- In patients with  $NPI < 14$ 
  - ▣ On placebo less agitated compared to drug

# Ballard (2004)

- Less likelihood of behaviours emerging if drug withdrawn in patients with  $NPI < 14$
- Concluded most patients with stable behaviour and 3 months of treatment can have drug discontinuation
- Did highlight the study settings

# DART-AD (Ballard 2008)

- 165 patients over 65yo with Alz Dementia
- Multiple centres
- MMSE > 6 or SIB > 30
- No individual NPI score >7
- On antipsychotic for at least 3 months
- Double blind randomised trial
- Medication withdrawal
- Very low, low or high dose

# DART-AD (BALLARD 2008)



# DART-AD (Ballard 2008)

- Placebo (82) versus active (83) treatment
- Primary outcome
  - ▣ Was antipsychotics associated with an accelerated cognitive decline as measured by SIB
- Secondary outcomes
  - ▣ MMSE
  - ▣ NPI
- Baseline, (1 m), (3m), 6 months, 12 months

# DART-AD (BALLARD 2008)

---

---

Assessment	Pretreatment Screening	Baseline	1 Month	3 Months	6 Months	12 Months
SIB	—	✓	—	—	✓	✓
SMMSE	✓	✓	✓	—	✓	✓
FAS	—	✓	—	—	✓	✓
BADLS	—	✓	✓	—	✓	✓
STALD	—	✓	—	—	✓	✓
NPI	✓	✓	✓	✓	✓	✓
FAST	—	✓	—	—	✓	✓
M-UPDRS	—	✓	—	—	✓	✓
CGIC	—	—	—	—	✓	✓

---

doi:10.1371/journal.pmed.0050076.t002

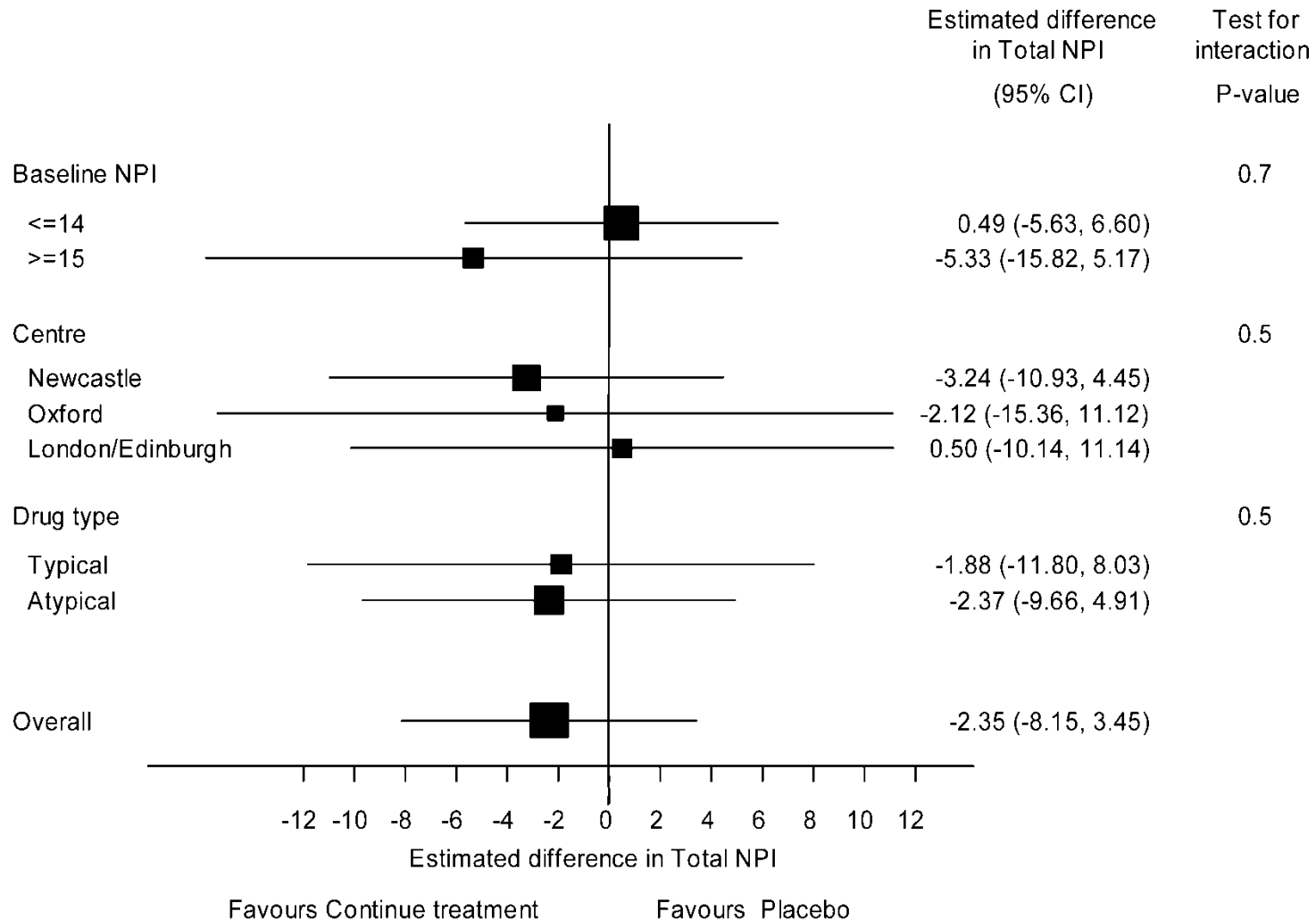
# DART-AD (Ballard 2008)

- Many did not start or lost to follow up
- 51 in each group analyzed at 6 months
- 14/51 discontinued placebo and 11/51 discontinued active treatment
- 3/51 discontinued placebo and 3/51 discontinued active due to behaviour

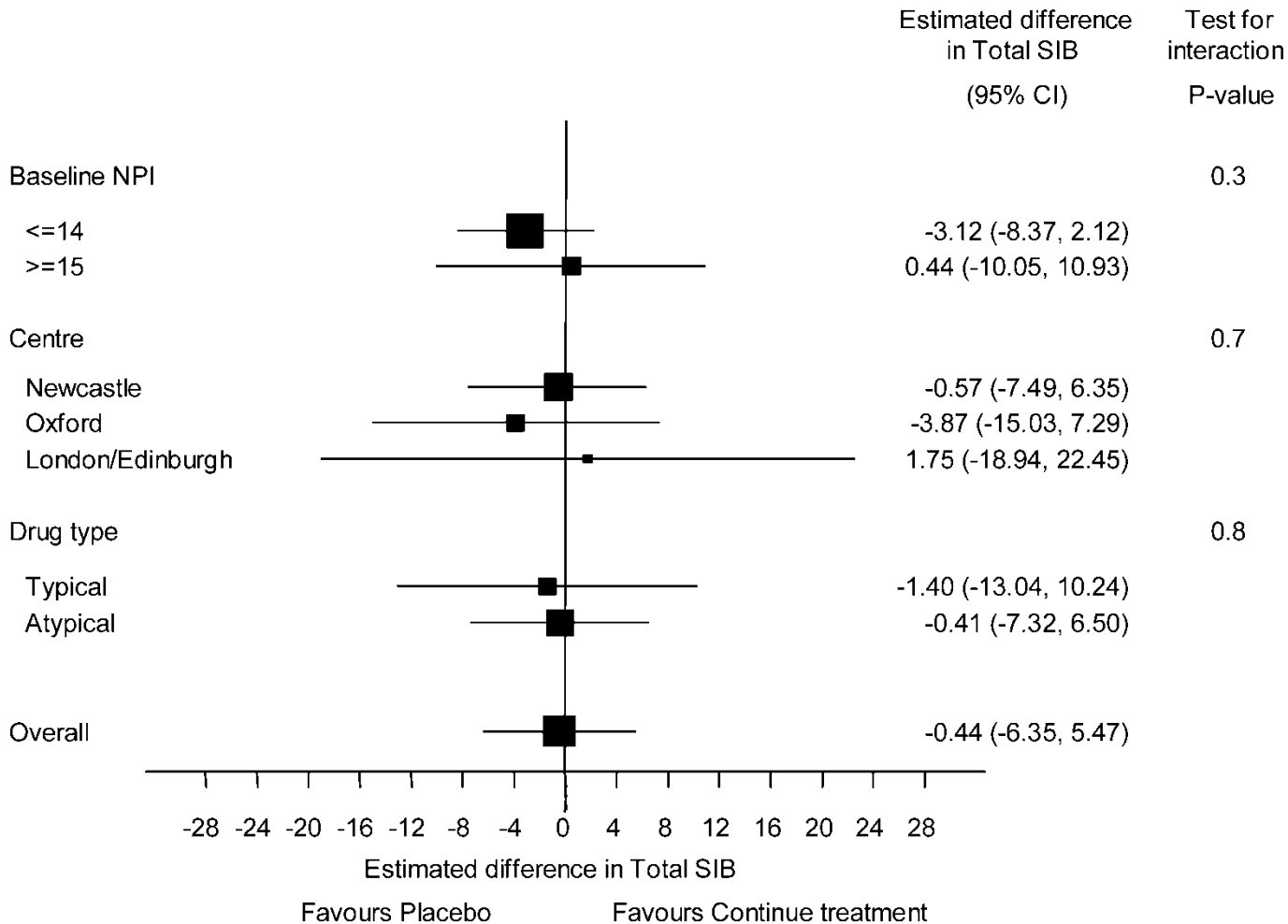
# DART-AD (Ballard 2008)

- Six months outcome
- No difference in estimated SIB changes (5.7 point deterioration placebo v 6.2 active)
- No difference in estimated mean changes in NPI
  - ▣  $\text{NPI} \leq 14$  changes similar
  - ▣  $\text{NPI} > 14$  five point NS advantage for active
- No difference in SMMSE

# DART-AD (BALLARD 2008)



# DART-AD (BALLARD 2008)



# DART-AD (Ballard 2008)

- 12 month data limited
- No significant difference in estimated mean SIB changes
  - ▣ 27 placebo and 28 active treatment
  - ▣ 8.5 deterioration placebo v 16.5 active treatment
  - ▣ estimated mean difference in deterioration favouring placebo -8.4 adjusted for baseline

# DART-AD (Ballard 2008)

- Significant difference in estimated mean NPI changes
  - ▣ 31 placebo and 28 active treatment
  - ▣ 11.4 deterioration placebo v 1.4 active treatment
  - ▣ estimated mean difference in deterioration favouring active treatment -10.9 (-20.1, -1.7) adjusted for baseline
  - ▣ NPI  $\leq$  14 no difference
  - ▣ NPI  $>$  14 -16.9 advantage (-32.5, -1.2)

# DART-AD (Ballard 2008)

---

- Underpowered as problems with recruitment
- Sometimes antipsychotic indication not clear

# Issues

- Are the patients not referred or excluded for trial participation any different?
- Tapering antipsychotics versus suddenly stopping them- is there a difference?
- To what degree does staff “buy in” affect outcome?
- To what degree does research or specialist participation affect outcome

# Conclusions

- Good evidence that antipsychotics can be stopped for patients with BPSD in dementia
- If patients are stable residents and have no or a low level of symptoms
- However, jury is out on higher levels of symptoms, but not an impossibility
- How do we translate this advice to primary care and provide support?



THANK YOU!