Drug treatment of cancer-related fatigue…an example of the difficulties of undertaking a Cochrane review

Dr Paddy Stone

Reader in Palliative Medicine

St George's University of London

Acknowledgments

- Dr Ollie Minton
- Prof Michael Sharpe
- Prof Matthew Hotopf
- Prof Alison Richardson

Overview

- Background to systematic review
- Process of undertaking review
  - Difficulties with methodology
- Results
  - Difficulties with extrapolation of results
- Lessons learned
  - Systematic reviews…what they can and what they can't do

Background

- Cancer related fatigue is a prevalent symptom which is under recognised and difficult to treat
- Drug therapy represents one potential treatment option
- There are conflicting data from intervention studies depending on population studied and outcome measures used

Previous evidence

- Non-systematic reviews have previously suggested a role for corticosteroids, progestational steroids, antidepressants, erythropoietin, ondansetron, methylphenidate and modafinil
- The National Comprehensive Cancer Network (NCCN) guidelines suggest the pharmacological treatment of anaemia, insomnia and the use of methylphenidate, (modafinil), corticosteroids (and progestational steroids) based on data from cancer and non-cancer studies and using qualitative rather than quantitative data synthesis

Objectives

- To evaluate the effectiveness and adverse events related to drugs used in the treatment of CRF at all stages of cancer treatment (including palliative care) compared with standard care or non-pharmacological interventions
- To establish optimal dose and duration of drug therapy(s)

Resources

- Personnel
  - Full-time research fellow
  - Four co-authors
- Time
  - Six months full-time equivalent, one year total
  - One week training course
- Infrastructure
  - Computer and E-Journal access
  - Endnote bibliographic database
  - Revman systematic review software
  - Statistical and methodological support from Cochrane centre and from Clinical Effectiveness department St George's Hospital
- Financial
  - NCRI Supportive and Palliative Care Research Collaboratives Capacity Building Grant - Euro 100k

Inclusion criteria

- Randomised controlled trials
- All stages of cancer…included patients on treatment, disease-free survivors and palliative care
- Drug therapy versus placebo or standard care or other non-pharmacological intervention
- Improvement of fatigue had to be a prior stated aim

Exclusions

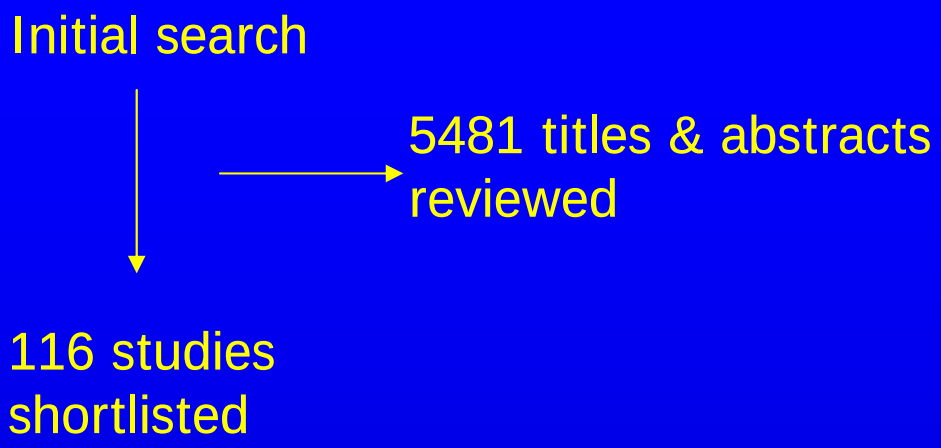
- Studies comparing different types of cancer-modifying treatment (e.g. chemotherapy regimens or radiotherapy) and their effect on prognosis and quality of life ?

Search strategy

- Very broad
  - "Cancer" terms AND "Fatigue" terms
  - Hand searching
  - Reference lists
  - Experts
  - Authors
- Not a search for specific drugs

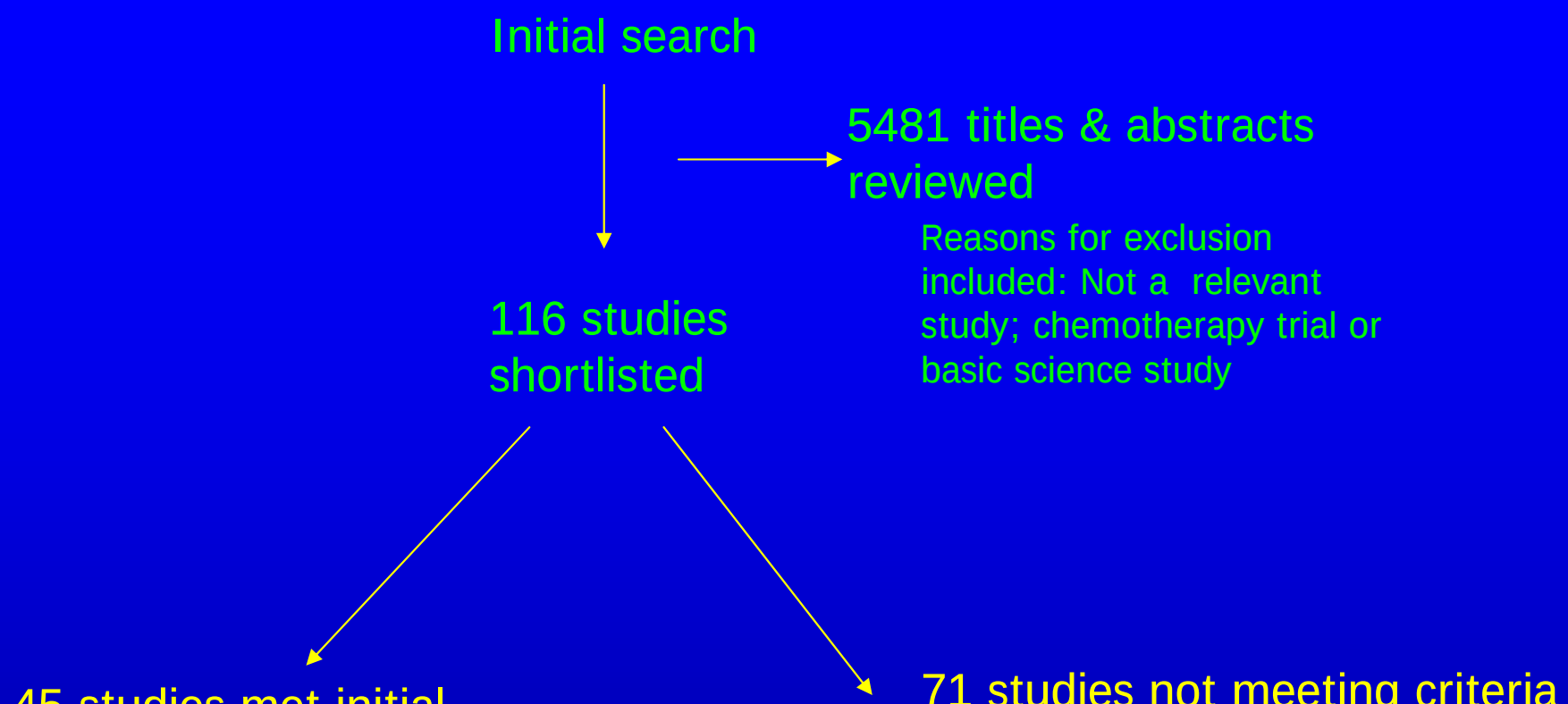
Problems in study selection

- Identifying prior stated aims – some studies used quality of life and fatigue as interchangeable terms


Initial search
5481 titles & abstracts reviewed
116 studies shortlisted

Studies excluded on initial screening

- Chemotherapy studies, basic science studies
- Large numbers of fatigue studies were open label, non randomised, case reports, case series etc…
- Many studies undertaken in palliative care population fell into this category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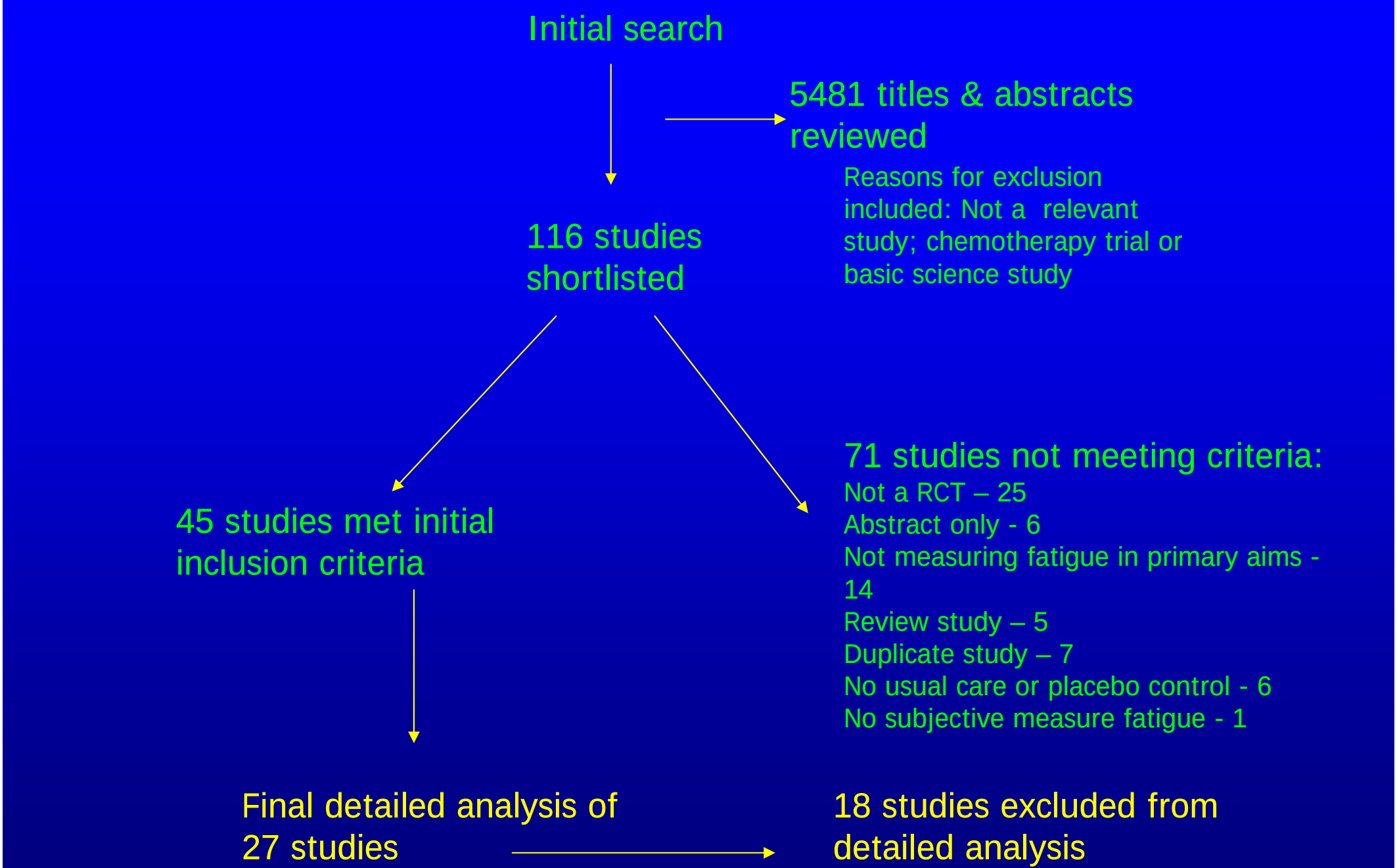
116 studies shortlisted
45 studies met initial inclusion criteria
71 studies not meeting criteria

Studies excluded on closer scrutiny

- Not a RCT – 25
- Not reporting fatigue as a primary aim – 14
- Duplicate study – 7
- Abstract only - 6
- No usual care or placebo control - 6
- Review study – 5
- No subjective measure fatigue - 1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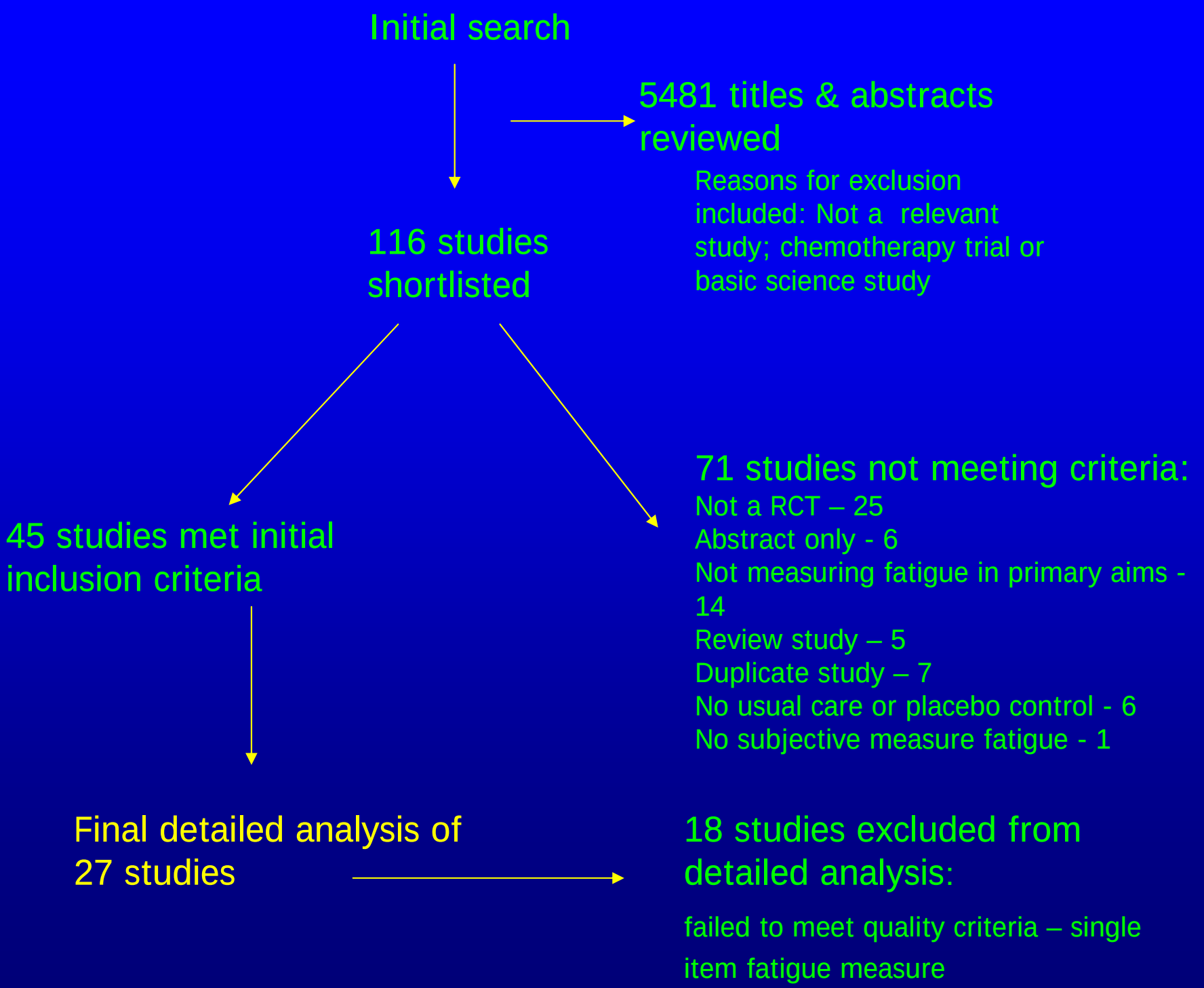
45 studies met initial inclusion criteria
Final detailed analysis of 27 studies
18 studies excluded from detailed analysis

Why exclude 18 studies?

- A post search results decision was made to exclude single item outcome measures – These included:
  - Quality of life measures (such as the FACT-G) containing only one item relating to fatigue
  - Single Visual Analogue Scales (VAS)
- Why exclude studies using single item fatigue scales?
  - Fatigue is a complex symptom for which single item scales lack face validity
  - Doubt about whether fatigue was truly a prior stated aim if outcome measure was only a single item
  - Inclusion may have introduced unacceptable bias
- These studies are specifically mentioned within the review (as they meet our ***a priori*** inclusion criteria) but are not analysed in detail

Single item studies

- 18 studies involving 3827 participants
- Among those studies not analysed further
  - Corticosteroids (two old studies)
  - A number of Erythropoietin studies
  - Adenosine tri-phosphate infusions
  - Miscellaneous drugs – fluoxetine, fish oils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failed to meet quality criteria – single item fatigue measure

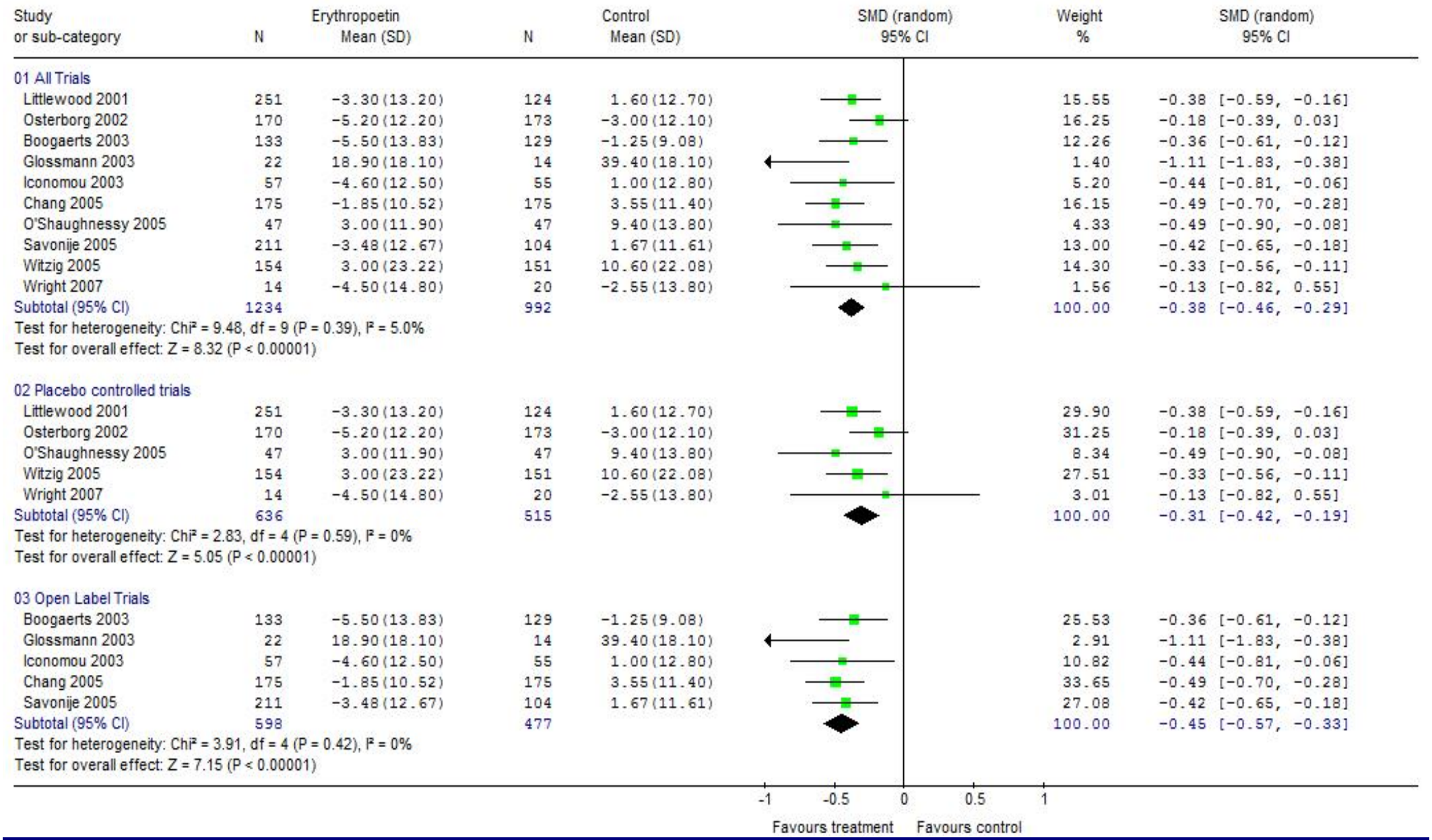
Results

- Four main drug classes
  - Haemopoetic growth factors
  - Psychostimulants
  - Progestational steroids
  - Antidepressants
- Two single studies
  - Ibandronate
  - Etanercept

Results

- For detailed discussion of results please listen to Dr Minton presentation at 14:00 Friday 31st May (Lillesalen room)

Review: Drug therapy for the management of cancer related fatigue (Version 04)
Comparison: 01 Erythropoetin versus no intervention (subanalysis versus placebo)
Outcome: 01 Difference in fatigue score



Difficulty with interpreting results

- Haemopoietic growth factors
  - Anaemic cancer patients on chemotherapy
- Methylphenidate
  - Small number of participants
  - One study showed no benefit over placebo
  - All tumour types, on or off treatment, 1-8 weeks
- Progestational steroids
  - Any tumour type, 4 studies, 587 participants
  - Off treatment
  - 1 – 12 weeks
- Anti-depressants
  - Paroxetine does not prevent fatigue in outpatients receiving chemotherapy

General limitations

- It is possible that all trials have not been published or identified
- Absence of evidence is not the same as evidence of absence
  - Corticosteroids?
  - Modafinil?

General benefits

- Transparent process throughout
- Minimise personal opinion
  - results different from previous reviews
- Quantitative
- Reproducible

Systematic reviews – what they can and can't do

- Can do
  - Best method of synthesising studies
  - Identify gaps in research base
- Can't do
  - Garbage in…garbage out
  - Nothing in…nothing out