Systematic review of chronic pelvic pain and IBS clinical trials: Pain outcome measures and inclusion criteria

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Objective

Summarize eligibility criteria and outcome measures from previous RCTs to inform design recommendations for future trials

Methodological challenges

- Multiple symptoms (controlling false positive rates)
- Sometimes include recurrent pain, pain affected by other symptoms, activity-specific pain
- Many potential causes of lower abdominal pain (e.g., cancer, infection) to rule out
- Overlapping conditions

Presentation outline

- Outline systematic review methodology / trial characteristics
- Summarize trial inclusion / exclusion
- Summarize primary outcome measures and endpoints
- Summarize methods used to adjust for multiplicity

Contributors

Research design characteristics of published randomized clinical trials for irritable bowel syndrome and chronic pelvic pain conditions: an ACTTION systemic review.

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Manuscript in preparation

Systematic Review search

Conditions
- Irritable bowel syndrome (IBS)
- Chronic prostatitis (CP)
- Interstitial cystitis (IC)
- Vulvodynia
- "Chronic pelvic pain"

Search strategies
(1) Condition names (with synonyms) AND "pain" [RCT filter]
(2) Condition names (with synonyms) AND FDA/EMA-approved drugs [RCT filter]

Inclusion criteria
- Randomized clinical trial
- Pharmacologic treatment
- Treatment for 1 of the conditions or for "chronic pelvic pain" with no specified etiology
- Double-blinded
- At least 1 pain-related outcome reported in the abstract
  - Includes "discomfort"

Search results
- Search 1 → 121 articles
- Search 2 → 2 additional articles
  - **123 identified articles (124 trials)**

Characteristic	Frequency (%)
Condition	
Irritable bowel syndrome	84 (68)
Interstitial cystitis	18 (15)
Chronic prostatitis	16 (13)
"Chronic pelvic pain"	4 (3)
Vulvodynia	2 (2)
Year published	
1973 - 2000	31 (25)
2001 - 2016	93 (75)
Type of treatment	
Putative pain mechanism (e.g, anti-depressants)	32 (26)
Other (e.g., anti-constipation, anti-diarrhea)	92 (74)
Sponsor	
Industry	78 (63)
Industry only provided treatment	12 (10)
Other	34 (27)

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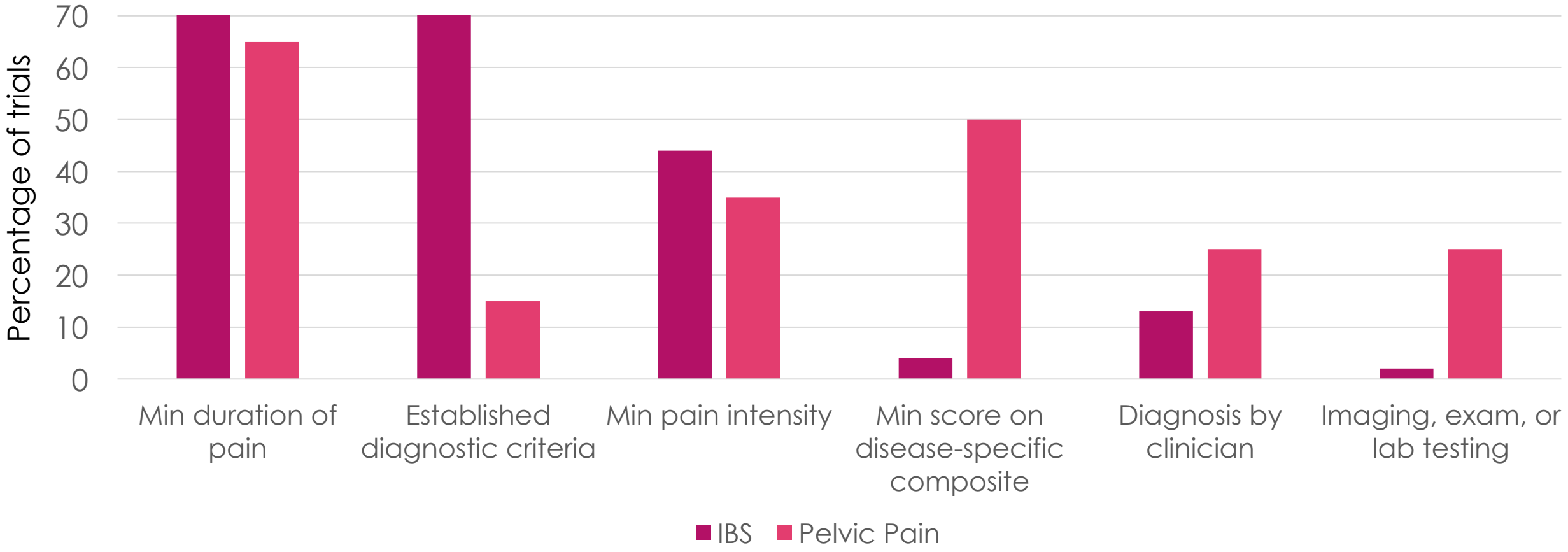
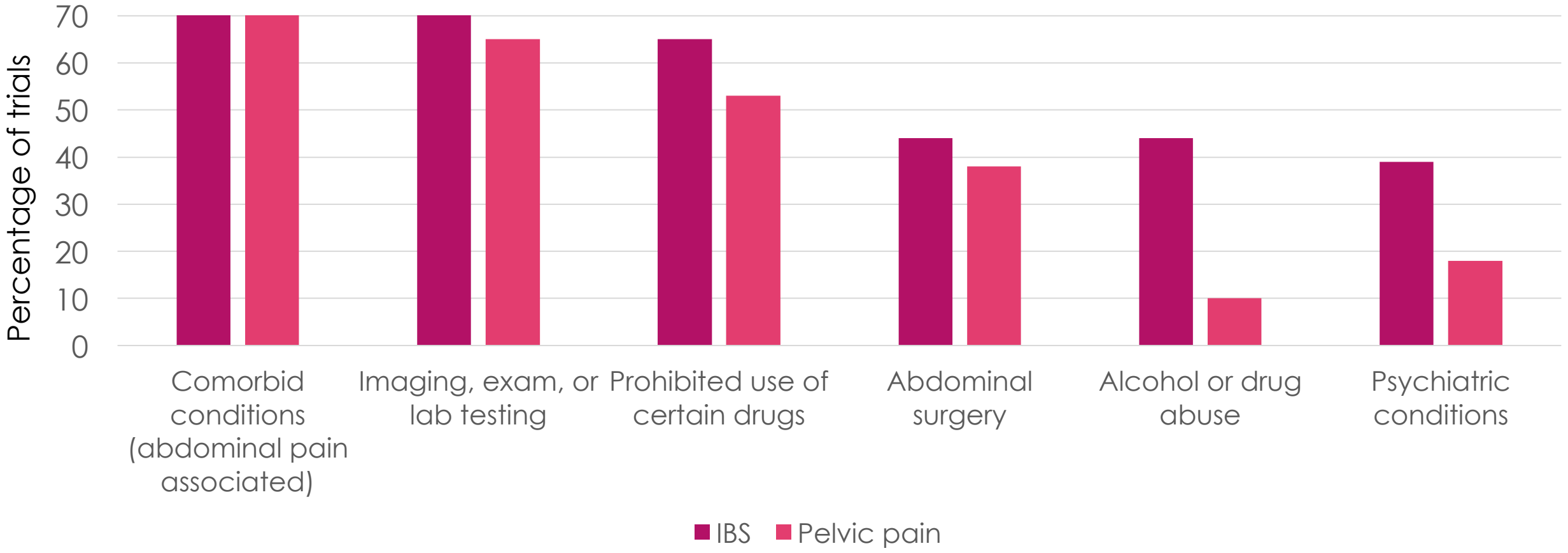
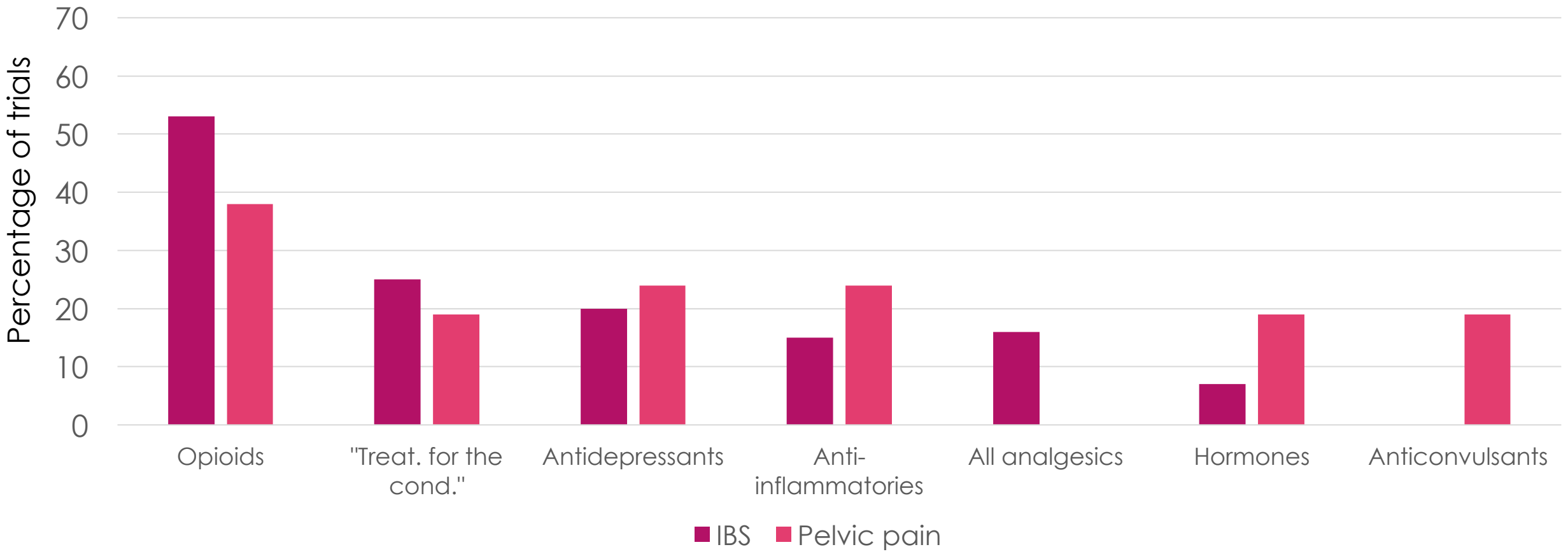
Inclusion Criteria



Exclusion Criteria



Prohibited drugs



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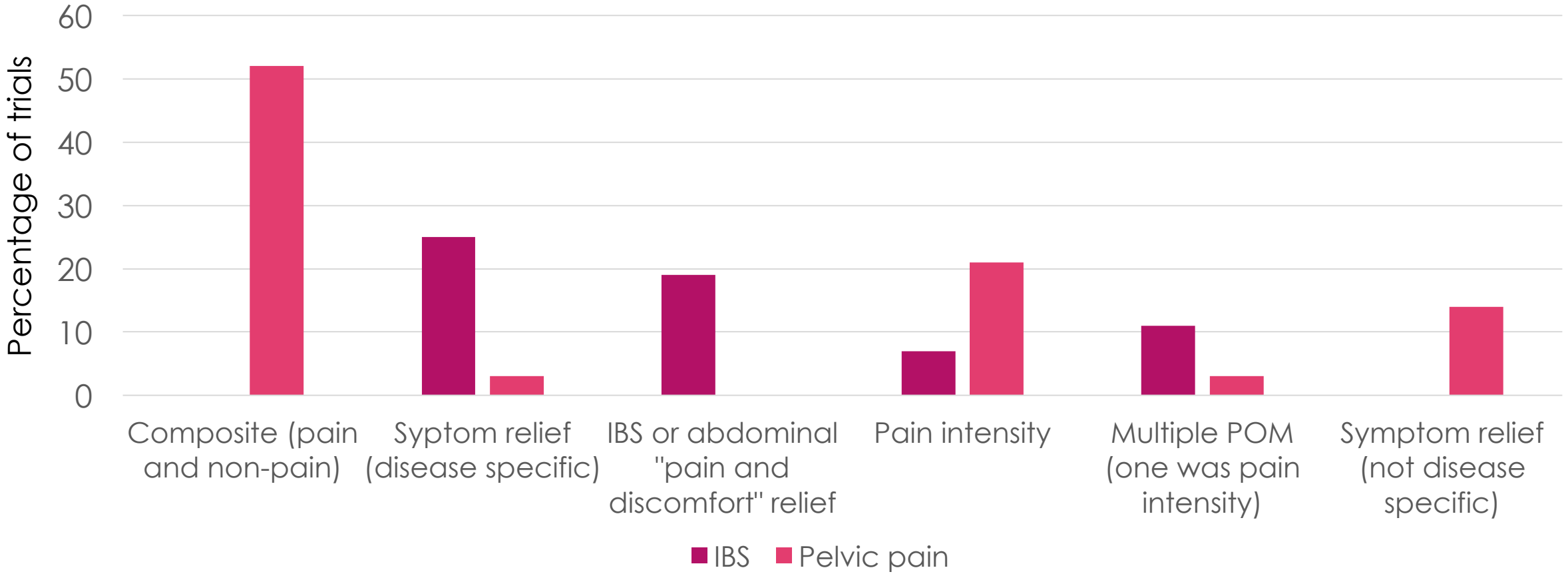
Reporting – primary outcome measures and endpoints

- 86 (69%) identified one or multiple primary outcome measures
  - E.g., 0 -10 pain numeric rating scale
- 67 (54%) identified a single primary endpoint
  - E.g., Response, defined as 30% improvement in pain intensity at trial endpoint

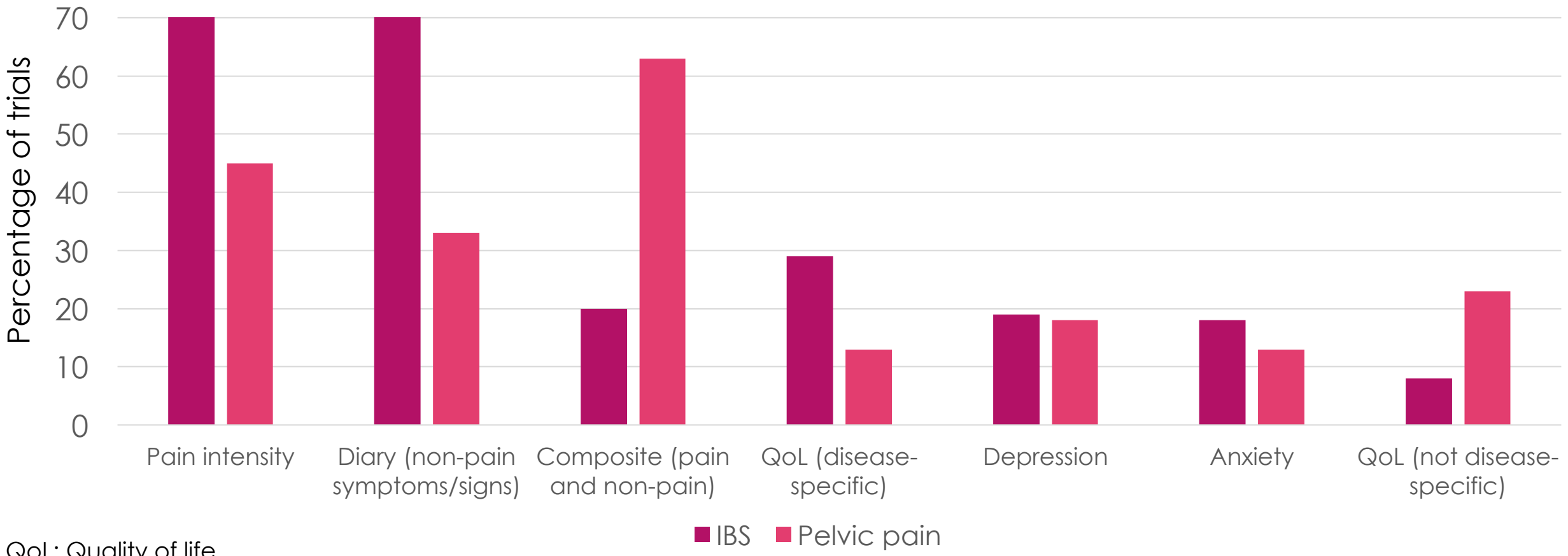
- These numbers are used for the denominator in the percentages presented in the graphs and tables for primary outcome measures and endpoints

Primary outcome measures



Primary outcome measure (POM)

Non-primary outcome measures



QoL: Quality of life

Primary endpoints

"Response" endpoints – based on a certain percentage of time

"Response" definition	IBS	Pelvic Pain
Adequate pain relief for a certain percentage of time	9 (20%)	0 (0%)
Adequate "IBS symptom relief" for a certain percentage of time	9 (20%)	0 (0%)
Adequate pain relief AND improved bowel movements for a certain percentage of time	4 (9%)	0 (0%)
Adequate improvement in stool consistency for a certain percentage of time	1 (2%)	0 (0%)

"Response" endpoints – based on single time point (e.g., endpoint week)

"Response" definition	IBS	Pelvic Pain
Adequate symptom relief at endpoint	3 (7%)	3 (14%)
Adequate improvement (or % improvement) in pain and non-pain composite outcome measure at endpoint	1 (2%)	3 (14%)
Adequate improvement in stool consistency at endpoint	1 (2%)	0 (0%)

Primary endpoints, cont.

Severity endpoints

Endpoint	IBS	Pelvic Pain
Severity or change from baseline in pain at endpoint	2 (4%)	5 (24%)
Severity or change from baseline in pain and non-pain composite at endpoint	0 (0%)	7 (33%)
Stool consistency or constipation at endpoint	2 (4%)	0 (0%)
Biomarker at endpoint or change from baseline	2 (4%)	9 (0%)

Miscellaneous endpoints

Endpoint	IBS	Pelvic Pain
Model that incorporates relief or improvement over time (e.g., RM-ANOVA)	3 (7%)	0 (0%)
Summary of change in pain intensity at a specified time after receiving a dose of experimental medication	1 (2%)	1 (5%)
Other (reported for 1 trial each)	7 (15%)	2 (10%)

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Adjustment for multiplicity

- 71 (57%) did not identify a primary analysis
- 44 (35%) identified 1 primary analysis
- 9 (7%) identified multiple primary analyses
  - 7 adjusted for multiplicity
    - Gate keeping strategy (n=5)
    - Bonferroni (n=1)
    - Combination of gatekeeping and Bonferroni (n=1)

Conclusion

Review identified

- Variability in entry criteria and outcome measures
- Deficiencies in identifying single primary analyses or adjusting for multiplicity
- Multiple examples of methods to combine symptoms into single endpoints or adjust for multiplicity
  - Responder definitions based on improvement in multiple symptoms
    - Varying time frames considered (response at endpoint vs. specified percentage of time)
  - Composite outcome measures
  - Gatekeeping approaches
  - Bonferroni correction

Other methods to control false positive rates

- Co-primary analyses (both require a p-value < 0.05)
- Step-wise procedures that are related to Bonferroni (e.g., Holm) (less strict)
- Methods that rank participants based on their combined treatment response on multiple outcome measures (e.g., DOOR (Evans, *Clinical Infectious Diseases*, 2015))

DOOR (Desirability of Outcome Rating)

1. >50% improvement in pain AND no rescue medication
2. >50% improvement in pain BUT rescue medication taken on >20% of days
3. <50% improvement in pain BUT no rescue medication taken
4. <50% improvement in pain AND rescue medication taken on >20% of days

   - Can add finer gradations

DOOR, cont.

DOOR Probability - Probability that a randomly selected patient in Arm A has a ***more desirable*** outcome than a patient in the control arm (+half credit for ties)

Advantages:

- Uses outcomes to analyze overall patient experience rather than patients to analyze individual outcomes
- Appealing "probability" interpretation
- Deals with competing outcomes
- May have more power than a dichotomous composite responder analysis

Limitations:

- Developing a ranking scheme may be challenging
- Differences may be driven by difference in single outcome measure (similar for any composite)

Thank you!

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