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A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes : ACCRU study SC-1603

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Disclosures

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The Hot Flash Problem

Hot flashes are common
Affect 75% of midlife women
Can persist for 15+ years

Negatively impact quality of life
Interfere with many spheres of life: work, sleep, relations, sexuality, social and leisure activities.

Breast cancer survivors are at higher risk
Hot flashes often longer term and more severe, due to chemo-induced menopause, anti-estrogens, OFS

Can affect breast cancer outcomes
Hot flashes can interfere with adjuvant therapy compliance and persistence

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Available HF therapies

Not all patients respond to these measures.

Hormone replacement

Most effective

Not recommended when there are concerns for breast cancer

Non-hormonal agents

SSRIs, SNRIs, anticonvulsants

Efficacy supported by several randomized trials

Non-pharmacologic therapy

Lifestyle and behavioral interventions

Limited data

Loprinzi et al, Lancet 2000; Loprinzi et al, JCO 2002; Barton et al, JCO 2010; Stearns et al, JAMA 2003; Guttuso et al, Obstet Gynecol2003; Gordon et al, Menopause 2006; Freeman et al, JAMA 2011

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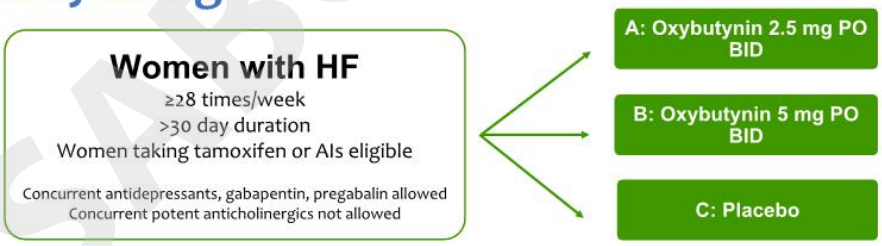
Oxybutynin

- **Anticholinergic** (oral or transdermal).
- FDA approved for overactive bladder (5-20 mg daily).
- **"Decreased sweating" common** → effective for hyperhidrosis.
- **Data in refractory hot flashes:**
  - **Retrospective study:** Sexton et al, Menopause, 2007.
  - **Prospective study:** Simon et al, Menopause, 2016. Oxybutynin XR 15 mg/d improved HF but with toxicity. Investigators recommended studying lower doses.

Study design



Treatment duration = 6 weeks, after a baseline week without medication (questionnaires)

Weekly questionnaires:
Hot Flash Diary
HFRDIS
Symptom experience questionnaire

Endpoints:
Primary: Intra-patient change in weekly HF score[1] and frequency
Secondary: change in HFRDIS, change in self-reported symptoms

[1]Sloan et al, JCO 2001

Statistical considerations

- **Primary endpoint:** Time-averaged intra-patient changes in HF score from baseline during the treatment period were compared between treatment and placebo arms using a repeated measures model.
  - **Hot flash score:** frequency of each HF grade by the severity of the HF (G1= mild, G2= moderate, G3= severe, G4= very severe).
- **Secondary endpoints:** summarized by descriptive statistics and then compared using Wilcoxon rank sum tests, two sample t-tests, or chi-square tests.
- **Stratification factors:** age (18-49 vs 50 or older), concurrent tamoxifen use, concurrent aromatase inhibitor use, HF duration (<9 vs >9 months), and average baseline HF frequency per day (4-9 vs ≥10).

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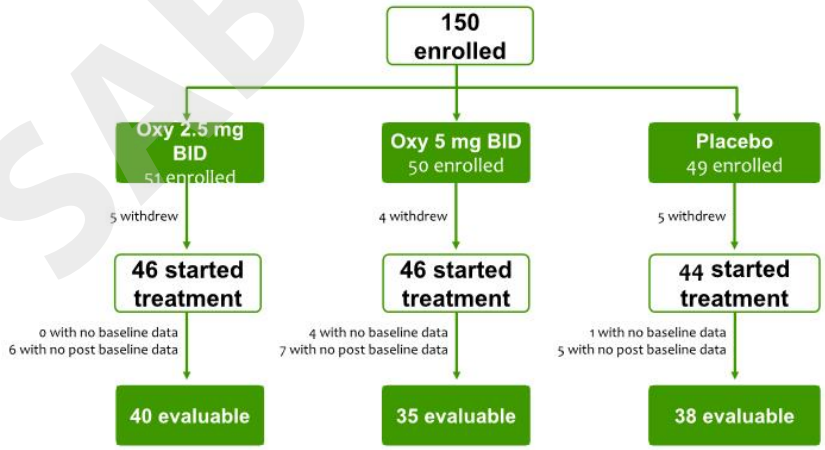
Consort diagram



Results – Baseline characteristics

	Oxy 2.5 mg BID (n=40)	Oxy 5 mg BID (n=35)	Placebo (n=38)	P-value
Mean age, years	56	58	58	0.40
Age group				
18-49	23%	17%	16%	0.72
>49	78%	83%	84%	
Concurrent AI*	38%	31%	34%	0.86
Concurrent Tamoxifen*	23%	37%	32%	0.38
HF duration				
< 9 months	23%	23%	18%	0.87
≥ 9 months	78%	78%	82%	
HF freq at enrollment				
4-9 HF/day	50%	54%	58%	0.79
≥ 10 HF/day	50%	46%	42%	
Baseline HF score				
mean (SD)	16 (10)	20 (17)	20 (12)	0.29
Baseline HF freq				
mean HF/d (SD)	8 (4)	10 (8)	10 (5)	0.49

* Duration of AI and tamoxifen was similar between arms

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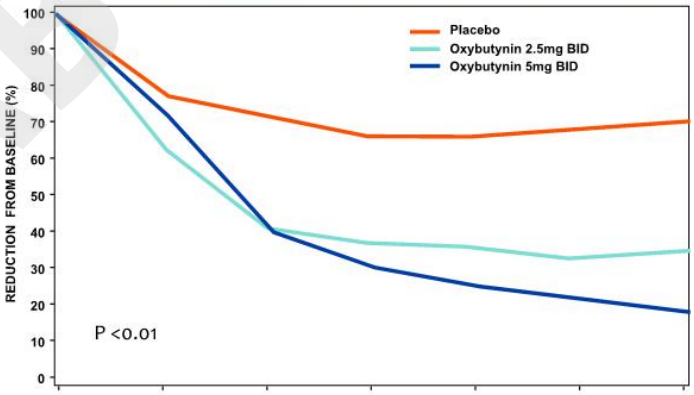
Results: Mean Hot Flash Score % Reduction from Baseline

HF Score = HF frequency x average severity

G1 = mild, G2= moderate, G3 = severe, G4 = very severe



WEEKS	Baseline	1	2	3	4	5	6
Placebo	38	38	38	37	35	35	35
Oxybutynin 2.5 mg BID	40	40	38	36	35	35	34
Oxybutynin 5mg BID	35	35	34	32	32	31	31

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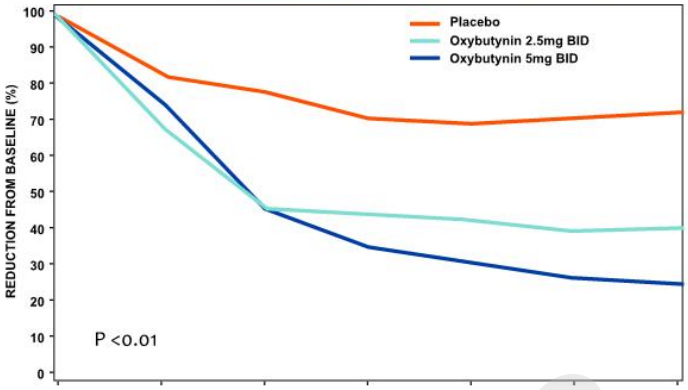
Results: Mean Hot Flash Frequency % Reduction from Baseline



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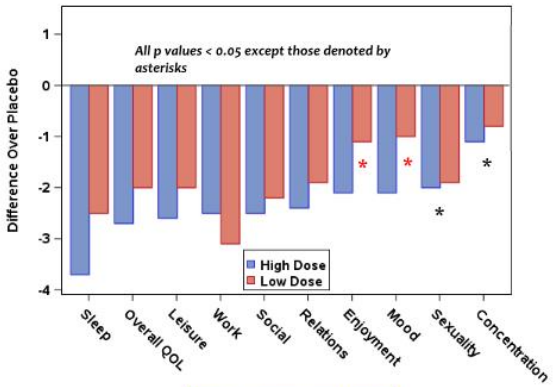
Results: Change in HFRDIS over placebo

Most HFRDIS measures were statistically better with oxybutynin than placebo, except:

- Not improved in either oxybutynin arm *
  - **Concentration**
  - **Sexuality**
- Not improved in oxybutynin 2.5mg BID *
  - **Mood**
  - **Life enjoyment**

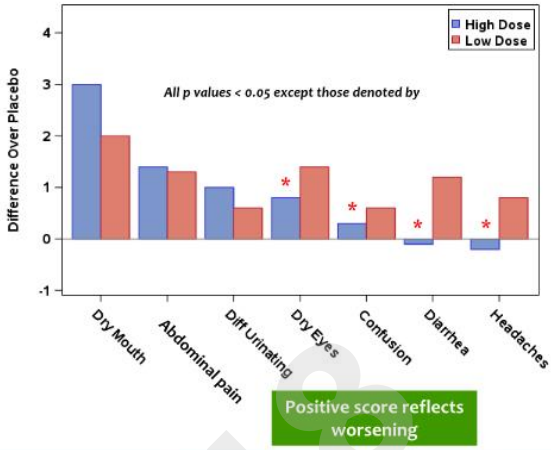


Negative score reflects improvement

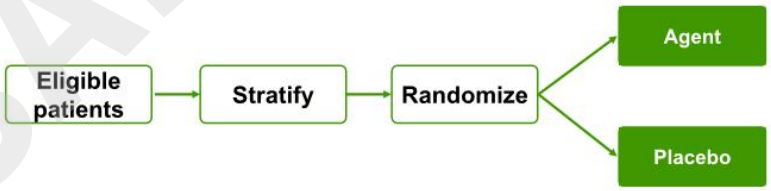
Results: Change in Baseline Symptoms Over Placebo

Both doses were generally well-tolerated:

- Symptoms worsened in both oxybutynin arms
  - **Dry mouth**
  - **Abdominal pain**
  - **Difficulty urinating**
- Symptoms worsened only with oxybutynin 5 mg BID
  - **Dry eyes**
  - **Episodes of confusion**
  - **Diarrhea**
  - **Headaches**



How does this compare with other HF trials?

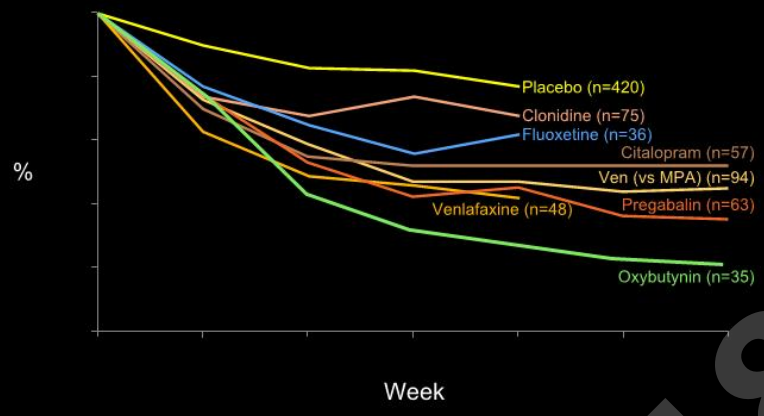


Basic study design of 13 phase III Mayo Clinic studies evaluating non-estrogenic medications for hot-flashes

Courtesy of Charles L Loprinzi

How does this compare with other HF trials?

Mean Hot Flash Score % Reduction Randomized Studies (positive trials)



Not superior to placebo:
- Soy
- Flaxseed
- Black Cohosh
- Mg oxide
- Vitamin E

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Conclusions

- Oxybutynin significantly improves HF frequency and severity.
- Use of oxybutynin is associated with positive impact in several quality of life metrics.
- Toxicity was acceptable.
- While the two oxybutynin doses were not formally compared, patients on 5 mg BID experienced more reduction in HF and improvement in more QoL measures.

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