GOOD EVIDENCE MATTERS

GEMs of the Week

SPOTLIGHT

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No Inferiority, No Problem: Amiloride Steps Up in Hypertension Care

Spironolactone vs Amiloride for Resistant Hypertension: A Randomized Clinical Trial

Lee CJ, Ihm SH, Shin DH, et al. Spironolactone vs Amiloride for Resistant Hypertension: A Randomized Clinical Trial. *JAMA*. 2025;333(23):2073-2082. doi:10.1001/jama.2025.5129

KEY TAKEAWAY: Amiloride is non-inferior to spironolactone as a fourth line agent for resistant hypertension and can be considered as an alternative treatment option.

STUDY DESIGN: Multi-site, prospective, open-label, blinded-endpoint randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Previous studies have demonstrated the efficacy of spironolactone, a potassium-sparing diuretic, as a fourth line agent for resistant hypertension. However, spironolactone is associated with anti-androgenic side effects and hyperkalemia. This study aimed to assess whether amiloride, another potassium-sparing diuretic that does not have anti-androgenic properties and is associated with decreased incidence of hyperkalemia, is non-inferior to spironolactone in the treatment of resistant hypertension.

PATIENTS: Adults with treatment resistant hypertension (defined as home measured systolic blood pressure [SBP] >130 mmHg

INTERVENTION: Amiloride 5 mg or 10 mg daily

CONTROL: Spironolactone 12.5 mg or 25 mg daily

PRIMARY OUTCOME: Change in home SBP measurement from baseline

Secondary Outcome: Achievement rate of home SBP <130 mmHg, incidence of hyperkalemia, incidence of gynecomastia

METHODS (BRIEF DESCRIPTION):

- Patients were adults 19–75 years old (mean age 55 years old, 37% women) from 14 sites across South Korea who had at least one in-office SBP measurement of 130–180 mmHg.
- 164 patients were enrolled and underwent a four-week run-in period on a fixed regimen including olmesartan, amlodipine, and hydrochlorothiazide. 118 patients were identified to have treatment-resistant hypertension
- They were randomly assigned to one of two groups:
  - The spironolactone group received a prescription for 12.5 mg per day, increased to 25 mg if SBP ≥130 mmHg and K^+ <5.0 mmol/L at week four.
  - The amiloride group received a prescription of 5 mg/day, increased to 10 mg under the same conditions.
- Both patients and their providers were aware of the group assignment.
- Patients were trained to use validated automated blood pressure (BP) monitors.
- Home BPs and labs including serum potassium, creatinine, and estimated glomerular filtration rate (eGFR) were evaluated by the provider at the four-week appointment, and dose adjustments were made as indicated.
- After a total of 12 weeks, patients collected home blood pressure readings.
- Investigators reinforced adherence at both four and 12-week check-ins with pill counts and patient reporting.
- The data was analyzed using a noninferiority framework with a margin of –4.4 mmHg and an intention-to-treat analysis.

INTERVENTION (# IN THE GROUP): 58

COMPARISON (# IN THE GROUP): 60

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- Amiloride did not significantly change home SBP measurement compared to spironolactone at 12 weeks (−13.6 mmHg vs −14.7 mmHg, respectively; between group difference −0.68 mmHg; 90% CI, −3.5 to 2.1).

Secondary Outcome –

- The amiloride and spironolactone groups achieved home-measured SBP <130 mmHg at rates of 66% and 55%, respectively, and achieved office-measured SBP <130 mmHg at rates of 57% and 60%, respectively, with no difference between the groups.

- There were no significant differences in cases of hyperkalemia or gynecomastia between groups.

LIMITATIONS:

- Patients were ethnically homogenous (all South Korean), potentially limiting the generalizability of the results.
- Neither patients nor providers were blinded to the treatment group.
- Patients collected their own BP readings.
- Chronic kidney disease (CKD) patients (GFR <50) were excluded from this study, although CKD is common in patients with resistant hypertension.
- This study did not compare the effects of the two drugs at higher (more commonly prescribed) doses.
- Using smaller doses with the relatively small sample size also makes it hard to assess/compare the side effect profiles of the drugs, which could impact with patient tolerance and adherence.
- There was a lack of long-term follow-up.
- No cases of gynecomastia in either group.

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To Tame the Urge or Lift the Strain: Botox vs Midurethral Sling in Women with Mixed Urinary Incontinence

Midurethral Sling vs OnabotulinumtoxinA in Females with Urinary Incontinence: The MUSA Randomized Clinical Trial

Harvie HS, Menefee SA, Richter HE, et al. Midurethral Sling vs OnabotulinumtoxinA in Females With Urinary Incontinence: The MUSA Randomized Clinical Trial. *JAMA*. 2025;333(21):1887-1896. doi:10.1001/jama.2025.4682

KEY TAKEAWAY: Intradetrusor onabotulinumtoxinA does not improve mixed incontinence symptoms compared to midurethral sling in women with mixed urinary incontinence nonresponsive to conservative measures.

STUDY DESIGN: Multicenter, single-blinded randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of blinding, short follow-up period, and use of per-protocol analysis)

BRIEF BACKGROUND INFORMATION: Mixed urinary incontinence, characterized by symptoms of stress and urge incontinence, is a common condition with age-associated increases in prevalence and impact on quality of life across all dimensions of well-being. There is a relative dearth of empirical research regarding the benefits and optimal sequencing of procedural interventions for women with unsuccessful response to conservative measures. This study aimed to explore the superiority of targeted management of urge urinary incontinence symptoms (intradetrusor onabotulinumtoxinA) over stress urinary incontinence symptoms (mid-urethral sling) in improving symptom burden in this patient population.

PATIENTS: Women with mixed urinary incontinence

INTERVENTION: Intradetrusor onabotulinumtoxinA

CONTROL: Mid-urethral sling

PRIMARY OUTCOME: Change in mixed urinary incontinence symptoms at six months

Secondary Outcome: Change in mixed urinary incontinence symptoms at three months; irritative and stress incontinence symptoms at six months

METHODS (BRIEF DESCRIPTION):

- The authors conducted a multicenter, single-blinded RCT across seven clinical sites, which included females with moderate to severe symptom burden from both stress and urge urinary continence for at least three months, as assessed through the Urinary Distress Inventory (UDI) questionnaire.
- Participants selected were women ≥21 years old who tested positive on the cough stress challenge, had at least four episodes of urge incontinence on a three-day bladder diary, and prior unsuccessful conservative treatment or oral pharmacotherapy.
- Patients were excluded if they had anterior or apical prolapse at or beyond the hymen and/or plan to undergo corrective surgery, prior sling, current overactive bladder medication or catheter use, and post-void residual volume of >150 mL on two occasions in the past six months.
- Patients were randomized 1:1 to receive intradetrusor onabotulinumtoxinA or mid-urethral sling.
    - Participations of both studies adhered to their assigned therapies for the first six months; following that, they had the option to switch to the alternate treatment or pursue a nonstudy option for the remaining six-month period.
    - The botox group was eligible for an additional injection between three to six months.
- The primary outcome was change in mixed urinary incontinence symptoms at six months, measured using the UDI questionnaire. Scores range from 0–300, with higher scores indicating greater severity of symptoms; MCID=26.
- Secondary outcomes were measured using the following:
    - Change in mixed urinary incontinence symptoms at three months was measured using the UDI questionnaire.
    - Change in stress symptoms was measured using the stress subscale of the UDI questionnaire. Scores range from 0–100, with higher scores indicating greater severity of symptoms; MCID=5.4.
    - Change in irritative symptoms was measured using the irritative subscale of the UDI questionnaire. Scores range from 0-100, with higher scores indicating greater severity of symptoms; MCID=10.

INTERVENTION (# IN THE GROUP): 71
COMPARISON (# IN THE GROUP): 66

FOLLOW-UP PERIOD: 12 months

RESULTS:

Primary Outcome –

- Intradetrusor onabotulinumtoxinA did not improve mixed urinary incontinence symptoms at six months compared to mid-urethral sling (mean difference [MD] 18; 95% CI, –4.6 to 41).

Secondary Outcome –

- Mid-urethral sling reduced severity of stress urinary incontinence at six months compared to intradetrusor onabotulinumtoxinA (MD 20; 95% CI, 8.4–32).
- Intradetrusor onabotulinumtoxinA did not improve mixed urinary incontinence symptoms at three months or irritative urinary incontinence symptoms at six months compared to mid-urethral sling.

LIMITATIONS:

- Neither the surgeons nor the participants could be blinded due to the nature of the study, potentially influencing both the administration of care and reporting of outcomes.
- Counseling regarding the availability of alternative treatments likely influenced patient expectations, resulting in a high crossover rate while underscoring the need for a combination approach to achieve desired clinical outcomes.
- Application of a per-protocol, as opposed to an intention-to-treat analytical strategy, can result in the introduction of selection bias and an overestimation of treatment efficacy.
- A longer follow up period is required to determine cross-over rates and long-term efficacy of repeated onabotulinumtoxinA injections.
- The study population was primarily composed of White, relatively healthy females without history of severe urogynecologic dysfunction, which may limit generalizability to more diverse or medically complex populations.

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Falling Short of Promise: Oxytocin Treatment Does Not Have Consistent Effects on Postpartum Depression

Oxytocin and Women Postpartum Depression: A Systematic Review of Randomized Controlled Trials

Zhu J, Jin J, Tang J. Oxytocin and Women Postpartum Depression: A Systematic Review of Randomized Controlled Trials. *Neuropsychiatr Dis Treat*. 2023;19:939-947. Published 2023 Apr 18. doi:10.2147/NDT.S393499

KEY TAKEAWAY: Oxytocin (OT) may not improve postpartum depression (PPD) compared to placebo in postpartum patients.

STUDY DESIGN: Systematic review of 4 randomized controlled trials (RCTs) (n=87)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample sizes, lack of meta-analysis, variation in study methods, and heterogenous results)

BRIEF BACKGROUND INFORMATION: PPD impacts approximately one in seven postpartum patients and constitutes a significant public health issue, impacting care of new parents and newborns. Research has produced mixed findings about the utility of oxytocin as a treatment method for PPD. This systematic review sought to evaluate the existing evidence.

PATIENTS: Patients with PPD within the first 12 months postpartum

INTERVENTION: Intravenous (IV) OT therapy

CONTROL: Placebo

PRIMARY OUTCOME: PPD and perceived infant behavior

METHODS (BRIEF DESCRIPTION):

- Accepted studies were RCTs involving postpartum patients assessing the impact of single-dose or weekly OT on PPD by measures of mental or emotional outcomes.
- This review excludes two of six studies in the original article because they did not evaluate maternal well-being but instead focused on maternal caregiving behaviors, and also did not perform any numerical analysis of results (Mah 2015 and Mah 2013).
- All four studies discussed in this report were assessed as having a low risk of bias.
- Patients were diagnosed with PPD by either using the Edinburgh Postnatal Depression Scale (EPDS), Beck's criteria, or Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.
- Patients varied between two weeks and 11 months postpartum.
- One dose of IV OT 24 international units (IU) was used in all but one study, which gave 16 IU OT daily for 12 weeks plus psychodynamic psychotherapy.
- Control groups received placebo, plus psychodynamic psychotherapy in the Clarici study.
- Three of the four studies used a crossover design.
- Various scales were used to assess impact on mood/emotions:
  - Positive and Negative Affect Scale (PANAS): Positive affect scores range from 10–50, with higher scores indicating more positive affect. Negative scores range from 10–50, with higher scores representing more negative affect.
  - Postnatal Negative Thoughts Questionnaire Baby-Related and Motherhood Negative Thoughts (PNTQ BRM-NT). Scores range from 0–51, with higher scores indicating more frequent negative thoughts.
  - Edinburgh Postnatal Depression Score (EPDS): Scores range from 0–30, with a score of ≥10 suggesting depression.
  - Hamilton Depression Rating Scale (HDRS): Higher scores on the HDRS indicate worse depression.
    - Normal: 0–7
    - Mild depression: 8–13
    - Moderate depression: 14–18
    - Severe depression: 19–22
    - Very severe depression: ≥23
- Scales were completed 30–45 minutes after treatment

INTERVENTION (# IN THE GROUP): 64

COMPARISON (# IN THE GROUP): 69

FOLLOW-UP PERIOD: 30–45 minutes post-treatment

RESULTS:

Primary Outcome –

- OT reduced the frequency of passive thoughts compared to placebo (1 study, n=20, mean PNTQ score 5.3 vs 2.1, respectively; *p*=.02)
- OT increased parental ratings of sorrow on SAM questionnaire compared to placebo (1 study, n=13; *p*=.01; no other numerical data provided).

- OT increased likelihood of describing infants as difficult compared to placebo (1 study, n=13; *p*=.038; no other numerical data provided).
- OT led to parents rating interaction with their infants as more parent-reported positive compared to placebo (1 study, n=13; *p*=.036; no other numerical data provided).
- OT did not have a significant effect on ratings of PPD compared to placebo (1 study, n=16; no statistical analysis completed).
- OT did not have a significant effect on positive and negative affect compared to placebo (1 study, n=26; no statistical analysis provided).

LIMITATIONS:

- Heterogenous study design and differing results between studies limit conclusions and prevent meta-analysis.
- Short follow up period limits assessment of longer-term efficacy.
- Variations in OT dose and schedule reduce comparability to others including RCTs.
- Sample sizes were small, which may obscure smaller effects.
- One study did not specify whether allocation was concealed, one study did not blind researchers, and two did not specify whether researchers were blinded, introducing potential for bias.

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