Is naltrexone/bupropion the missing piece for dose-sparing incretin therapy?

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Background: Obesity is a chronic, relapsing disease requiring sustainable long-term treatment. Incretin-based therapies are effective but limited by tolerability, access barriers, and cost. Adding naltrexone/bupropion (NB) may allow meaningful weight loss with lower incretin exposure.

Methods: We performed a retrospective chart audit of adults treated for obesity at a multidisciplinary clinic in Montreal, Canada (January–December 2025). For each strategy, the first four consecutive patients initiating out-of-pocket treatment were included: NB monotherapy, semaglutide monotherapy, tirzepatide monotherapy, semaglutide+NB, and tirzepatide+NB. Extracted variables included demographics, comorbidities, achieved medication doses, tolerability, and percent total body weight loss (TBWL) at 6 months. The primary outcome was mean achieved weekly incretin dose at 6 months; secondary outcomes examined sex-specific utilization.

Results: Twenty adults (12 women, 8 men; mean age 47 years; baseline BMI 36.6 kg/m²) were analyzed. At 6 months, NB monotherapy produced TBWL of 7.7% in women and 8.0% in men. Semaglutide monotherapy achieved 12.5% (women) and 13.5% (men), while tirzepatide monotherapy achieved 16.0% in both sexes. Combination therapy achieved comparable or greater outcomes: semaglutide+NB resulted in 14.5% TBWL in both sexes, and tirzepatide+NB produced 15.5% TBWL in women and 18.0% in men. Overall, 100% achieved ≥5% TBWL, 80% achieved ≥10%, and 45% achieved ≥15%. Mean achieved incretin doses were lower with combination therapy: semaglutide 2.23 vs 1.18 mg/week (−47%) and tirzepatide 11.9 vs 6.9 mg/week (−42%). Women stabilized at lower doses than men while maintaining similar weight loss.

Conclusion: Combination therapy supported clinically meaningful weight loss with marked dose-sparing incretin utilization.

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