

Oral Dosing of Progestogenic Androgens for Male Contraception Show Low Serum Testosterone and High Acceptability in Placebo-Controlled Trials

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A promising development in hormonal male contraception (HMC) is a class of bifunctional prodrugs that combine both androgenic and progestogenic activities into a single molecule. Examples of these prodrugs currently being studied are dimethandrolone undecanoate (DMAU) and 11 β -methyl-19-nortestosterone-17 β -dodecylcarbonate (11 β -MNTDC) (1, 2). The inactive prodrugs are cleaved to release active drug over a 24-hour timeframe, providing once-a-day dosing. As potent androgens, these steroids suppress gonadotropin secretion, leading to markedly decreased serum testosterone production and circulating levels. Low testosterone levels might lead to unpleasant symptoms of hypogonadism if DMAU and 11 β -MNTDC are not providing sufficient and effective androgenicity. Therefore, we examined the impact of the novel progestogenic androgens on serum testosterone levels and acceptability of varying dosages of these oral prodrugs in a secondary analysis of two Phase 1 placebo-controlled trials. Healthy male participants were randomized to take two or four oral pills of active drug or placebo per day. As DMAU and 11 β -MNTDC share similar mechanisms of action and tolerability, we examined the association of dosage as well as testosterone concentrations on combined drug acceptability versus placebo. Survey respondents across the two trials (39 DMAU, 30 11 β -MNTDC, 28 combined placebo group) shared similar baseline demographics. After seven days of usage, testosterone levels for those using either prodrug dropped to levels below 100 ng/dL while testosterone levels for those using the placebo (400-600 ng/dL) remained within the reference. Recipients of either DMAU or 11 β -MNTDC reported greater willingness to use the active prodrug in the future (75%), compared to placebo recipients (46.4%, $p=0.007$). Throughout the 28-day oral pill usage, while average testosterone levels during the period of suppression (day 7 to 28) were very low, they were significantly higher in the 200 mg group than in the 400 mg group (92.7 ng/dL vs. 49.6 ng/dL, p -value <0.001). Participants using 2 pills (200 mg, $n=33$) versus 4 pills (400 mg, $n=35$) of active drug did not report a significant difference in general satisfaction, willingness to use in the future, or recommendation of the study pill to other men ($p=0.85$, $p=0.48$, $p=0.60$, respectively). In placebo-controlled trials, men randomized to use active, daily oral progestogenic androgen prodrugs reported greater acceptability with their respective regimens than did men who received placebo pills despite low serum testosterone levels. Oral hormonal male contraceptive pill prototypes, DMAU and 11 β -MNTDC, significantly suppress serum testosterone while providing sufficient androgenicity to be acceptable to most men.

(1) Thirumalai et al. *J Clin Endocrinol Metab.* 2019; 104:423-32. (2) Yuen et al. *J Clin Endocrinol Metab.* 2020;105.

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