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Gender Studies Abstracts

Sex-specific exclusion criteria related to reproductive capacity in neuropathic pain randomized controlled trials

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INTRODUCTION

Neuropathic pain is a common condition that disproportionately affects individuals assigned female at birth. Population data indicate that people assigned female at birth are approximately 63% more likely to report neuropathic pain than those assigned male at birth (1). Clinical treatment guidelines for neuropathic pain are largely informed by meta-analyses that synthesize data from randomized controlled trials (RCTs). The design of RCT inclusion and exclusion criteria requires balancing internal validity alongside study generalizability. Historically, people with the capacity for pregnancy have been excluded from clinical research, often due to concerns about potential fetal risk (2). Although current recommendations emphasize inclusion unless clear scientific justification exists (3), concerns persist regarding disproportionate exclusion and burdensome contraceptive or pregnancy testing requirements. Understanding how participants with reproductive and childbearing potential are addressed in neuropathic pain RCTs is necessary to assess the applicability of trial evidence to a substantial portion of the affected population.

METHODS

We identified randomized controlled trials (RCTs) investigating pharmacologic and neuromodulatory interventions for neuropathic pain from a recent systematic review and meta-analysis (4). Two reviewers independently extracted and coded inclusion/exclusion criteria using a predefined, sex- and reproduction-related coding framework. Reviewers were trained and piloted the schema on 10% of trials. Interrater reliability was 95% ($\kappa = 0.78$), with disagreements resolved through discussion or a third reviewer. Criteria were coded based on language used in published manuscripts and trial registries. Trial-reported female-specific criteria were coded when studies referenced: (1) participants described as female of reproductive or childbearing potential; (2) pregnancy; (3) breastfeeding or lactation; (4)

contraceptive requirements for participants described as female; (5) pregnancy testing; or (6) exclusion of participants planning to donate ova. Male-specific criteria were coded when trials referenced: (1) reproductive restrictions for participants described as male; (2) contraceptive requirements; or (3) contraceptive requirements for partners. Trials could be coded for multiple criteria. Data were summarized using descriptive statistics.

RESULTS

Across 312 RCTs, 184 (59%) reported at least one female-specific reproductive exclusion criterion, while 15 (15%) reported at least one male-specific exclusion criterion. The most common female-specific criterion was current pregnancy or the requirement for a negative pregnancy test, reported in 172 trials (55%). Breastfeeding or lactation was listed as an exclusion criterion across 123 trials (39%), and 88 trials (28%) required participants described as female to use reliable contraception. Contraceptive requirements for participants described as male were reported in 15 trials (5%). Nine trials (3%) excluded all participants described as female of reproductive capacity, regardless of contraceptive use. Overall, reproductive exclusions were applied more frequently to participants described as female than to those described as male.

DISCUSSION

Our analysis of 312 RCTs found trial-defined female-specific reproductive exclusion criteria more common than male-specific criteria. Pregnancy-related exclusions appeared in over half of trials, while just over one-quarter required participants described as female to adhere to contraceptive requirements. Male-specific reproductive criteria were less common. These patterns may reflect longstanding regulatory and ethical frameworks focused on minimizing pregnancy-related risk. However, such practices may limit the generalizability of evidence to people with the capacity for pregnancy. Future research should explore whether these exclusions reflect true risks or precautionary practices that minimize research generalizability toward a substantial portion of the neuropathic pain population.

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