

IOM Workshop

Sex Differences and Implications for Translational Research

Depression Industry Perspective

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How and When Does Industry Consider Sex Differences in Depression?

- Sex-specific regulatory guidance
- Considerations in drug development (Ph 0- Ph 4)
- How Industry can help advance the understanding of these differences and their potential implications

1993 FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs

- Lifted restriction on participation of women of childbearing potential from entering Phase 1 and early Phase 2 trials, even before completion of all animal reproduction studies
- Include fair representation of both genders; collect and analyze gender-related data to detect clinically significant differences
- Collect pharmacokinetics data on demographic differences beginning in the Phase 1 and 2 studies. When feasible consider:
 - effect of the stages of the menstrual cycle
 - effect of exogenous hormonal therapy including oral contraceptives
 - effect of the drug or biologic on the pharmacokinetics of oral contraceptives

Additional Regulatory Considerations

- 2005 EMEA/CHMP review of ICH guidelines suggests no need for separate guideline on women
- FDA proposing revisions to labeling re: Pregnancy and Lactation
- Draft guidance for Lactation studies includes:
 - Drug under review expected to be used by women of reproductive age
 - Marketed medications commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

Pre-Clinical Considerations

- Sex differences in preclinical models related to stress / depression / anxiety have been described¹⁻³
- The vast majority of pharmacological experiments performed in males
 - Control effects of estrous cycle
- Animal models of mood and depression are limited
 - Do sex differences in animals translate forward?

1. Dalla et al. Basic & Clin Pharmacol & Tox 106, 226-233, 2009. 2. Ter Horst, GJ., et al . Physiol & Behavior. 97:239-249; 2009.
3. Goel N., Bale TL. Journal of Neuroendocrinology. 21(4):415-20, 2009.

Sex Differences in Pre-Clinical Toxicology

- Reproductive toxicology
- Teratogenicity
- Carcinogenicity

Industry Considerations of Sex Differences in Antidepressant Drug Development

- Phase I

- Often conducted in men, before the availability of reproductive tox, teratogenicity and carcinogenicity
- PK / ADME may differ
- DDI studies – oral contraception, tamoxifen

- Phase I-IV

- Inclusion criteria (design enrichment; requirement for birth control or abstinence)
- Pregnancy reporting
- Sex-specific reference ranges for labs & ECGs
- Sex-specific pharmacodynamic response
- Sex-specific ADRs

Industry Considerations of Sex Differences in Antidepressant Drug Development

- Phase II-III
 - Sex-specific indications (PMDD, VMS associated with menopause, Post-partum depression)
 - Indications *only in women* (GSK 561679 in MDD and PTSD)
 - Sub-group analyses and labeling
- Phase IV
 - Populations of interest
 - Investigator initiated studies
 - Epidemiological studies (eg. paroxetine label update re: CV malformations)
 - Pregnancy registries

What Can Industry Do?

- Advance personalized medicine by determining sex differences in dosing, efficacy and safety
- Develop and validate new pre-clinical models with better face, construct and predictive validity; study animals of both sexes
- Identify and evaluate sex-specific endophenotypes, and biomarkers for diseases and compounds
 - Increased stress-sensitivity¹
 - Sex-differences in tryptophan depletion studies²
 - Evaluate moderators and predictors of disease, resilience and treatment response
 - Sex-specific moderation by CRH receptor 1 gene on relationship between trauma and depression³
- Participate in cross-company /academia/NIMH collaborations and data sharing
 - Psychiatric GWAS Consortium; NA AED Pregnancy Registry

1. Hasler, G. et al., Neuropsychopharmacol. 29, 1765–1781, 2004 . 2. Neumeister, A. Psychopharmacol Bull. 37 (4):99-115, 2003.
3. Heim, C., Frontiers in Behavioral Neuroscience. 3 (41) 1-10, 2009.