

A spotlight on sex differences in neurological disorders

Despite the importance of incorporating sex as a variable in experimental and clinical studies being recognised by the US National Institute of Mental Health already in 2011, and subsequently by other funding agencies in the USA and Europe, substantial evidence gaps exist for sex differences in the epidemiology, clinical features, and pathophysiology of many neurological disorders. In 2001, The Institute of Medicine, a branch of the National Academy of Sciences in the USA, formed a committee to explore current understanding of sex differences and the biological underpinnings of these differences in human health. Their report, which was a seed for the National Institutes of Health's broad commitment to account for the role of sex in health, identified barriers to progress in research on sex-based differences. Recommendations to address these challenges included that sex-specific data should be more readily available, longitudinal studies should be conducted so that the results can be analysed by sex, and interdisciplinary research on sex differences should be encouraged. Yet, challenges remain today.

In *The Lancet Neurology*, Linda Stephen and colleagues review the management of epilepsy in women, describing the unique issues due to hormonal changes and family planning. Data collection in epilepsy pregnancy registries is essential for informing the care of women receiving antiepileptic drugs. However, despite known antiepileptic drug interactions with steroid hormones, potential for teratogenicity, and worse pregnancy outcomes among women with epilepsy compared with those without, there is an absence of contraceptive counselling for many women with epilepsy and a gap in knowledge of the underlying causes for their increased morbidity and mortality during pregnancy.

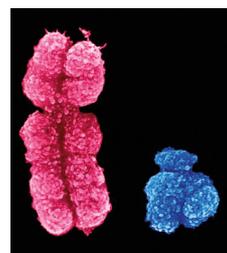
Family planning and pregnancy are pertinent issues across other neurological disorders as well, but the importance of data collection to inform neurologists on the safety of medications during pregnancy does not seem to have been consistently recognised. On Jan 5, 2019, consensus guidelines were published for the treatment of multiple sclerosis in pregnancy in the UK. While there are pregnancy registers in the UK specifically focusing on patients with multiple sclerosis taking dimethyl fumarate, teriflunomide, and alemtuzumab, the absence of large registry studies of the developmental outcomes of children

of women being treated for multiple sclerosis means that no comprehensive, up-to-date, central repository of information is available on best pharmacological management for these patients. The guidelines call for prospective data collection in a pregnancy register of all drugs and pregnancy-related outcomes in women with multiple sclerosis, pointing to the comparable role of epilepsy pregnancy registries.

The development of guidelines based on strong evidence needs not only prospective collection of data, but also a greater understanding of the implications of sex differences beyond family planning. In a Review of sex differences in migraine, while the safety of drugs in women with the disorder, in relation to contraception, pregnancy, and hormone replacement therapy, was identified as a priority to be addressed, the authors further underscored the potential for underdiagnosis of migraine in men because of a presumption that migraine is a female disorder. The predominance of women in clinical trials in migraine has led to a scarcity of data for men and thus suboptimal management. The authors note that treatment strategies do not differentiate between sexes, perhaps because the clinical trials informing practice did not adjust for sex.

A poor understanding of sex differences in neurological disease can lead to misconceptions and biases in management of male and female patients. Differences in management of stroke by sex have been discussed in another Review. The authors noted the importance of assessing sex differences in each aspect of the acute stroke evaluation process, but highlighted that differences in management strategies by sex are based on trials that have not been designed specifically to assess sex differences, have not adjusted for factors that might affect treatment and outcomes by sex, or were not adequately powered to identify sex-treatment interactions. Studies that have specifically aimed to evaluate sex as a modifier of outcome after treatment with thrombolysis have been inconclusive.

The recommendations of The Institute of Medicine in 2001 to facilitate research in sex differences and fill research gaps remain relevant today. Understanding sex differences should be a basic tenet of research from the mechanisms of disease to the clinical outcomes, to improve the diagnosis and management of neurological diseases for both sexes. ■ *The Lancet Neurology*



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For **The Institute of Medicine report** see <http://www.nationalacademies.org/hmd/~/media/Files/Report%20Files/2003/Exploring-the-Biological-Contributions-to-Human-Health-Does-Sex-Matter/DoesSexMatter8pager.pdf>

See **Review** *Lancet Neurol* 2019; published online March 8. [http://dx.doi.org/10.1016/S1474-4422\(18\)30495-2](http://dx.doi.org/10.1016/S1474-4422(18)30495-2)

For **consensus guidelines on pregnancy in multiple sclerosis** see *Pract Neurol* 2019; 0: 1–9

See **Review** *Lancet Neurol* 2017; 16: 76–87

See **Review** *Lancet Neurol* 2018; 17: 641–50