Sex-specifics of ECT outcome

INTRODUCTION

Major depressive disorder (MDD) currently affects more than 300 million people worldwide, equivalent to 4.4% of the general population with a female preponderance (Kuehner, 2017; WHO, 2018). Sex differences are observed in prevalence, severity, and outcome(Institute of Medicine Committee on Understanding the Biology of and Gender, 2001) and may etiologically be present due to sex differences in neurobiological, psychological or socio-cultural characteristics (Kuehner, 2017). Historically, exclusion of women in medication trials has led to unexpected side-effects in women(Liu and Mager, 2016). Sex should be recognized as an important variable in research, with sex-specific analyses of data. Despite sex differences and a lack of knowledge of possible negative outcomes in women, treatment for depression is typically administered in a one size-fits-all model and thus sex-specific clinical recommendations may add to improvement towards personalized application of ECT.

Regarding sex differences in prevalence, women are about twice as likely as men to develop lifetime depression(Kuehner, 2017; Liddon et al., 2018). This gap in depression rates emerges during mid-puberty and remains even at mid-age, whilst the prevalence of depression decreases in both sexes. Sex differences are encountered in the depressive phenotype in terms of symptom profiles and comorbidity. Women report both more and more severe key diagnostic symptoms for depression, depressed mood, appetite disturbance/weight changes, and sleep disturbances (Cavanagh et al., 2017; Kuehner, 2017). As for comorbid disorders, men show more externalizing disorders (e.g., substance abuse), whereas women report more comorbid internalizing disorders (e.g., anxiety disorders, somatoform disorders, eating disorders) and neuro-endocrine comorbidities including thyroid dysfunction(Cavanagh et al., 2017; Kuehner, 2017; Luppa et al., 2012).

Sex differences have been investigated for various antidepressant treatment modalities. In pharmacotherapy, there are known sex differences in pharmacodynamics, -kinetics and genetics (Dalla et al., 2010; Franconi and Campesi, 2014; Keers and Aitchison, 2010). Differences in metabolism and distribution of antidepressants result in higher serum levels of antidepressants, especially in older women. Influences on effectiveness due to these differences have not been proven, although it does explain sex differences in adverse effects and a lower dose suggestion for women(Keers and Aitchison, 2010).

ECT, as a biological treatment, is the most effective treatment in patients with severe MDD (Group., 2003). However, sex-specific research on the role of sex on effectiveness of ECT response is sparse (Fink, 2014). Two studies (n=176 and n=148, respectively), including patients with various major psychiatric diagnoses concluded that the ECT-induced clinical response is independent of sex

(Bolu et al., 2015; Manohar et al., 2017). However, including various psychiatric diagnoses may obscure the specific effect for patients with MDD. In a different study, Güney et al.(Güney et al., 2020) found in depressed patients treated with ECT (n=1066) the broader health-related quality of life outcome to be independent of sex. The improvement was the largest in older adults, who more often experienced psychotic features. While the broad outcome measure does provide an overall indication, it does not specifically address response.

Bloch et al. (Bloch et al., 2005) showed that depressed women received significantly fewer antidepressant drug trials compared to men before being referred to ECT (n=43). This pattern was in line with findings by Bolu et al. (Bolu et al., 2015). These results suggest that the sex-specific difference in presentation may lead to a different treatment, and/or that sex influences the decision-making process.

Regarding predictors of ECT response, two recent meta-analyses showed that sex is not a significant predictor, in contrast to older age, presence of psychotic features, shorter index episode, and medication resistance (Haq et al., 2015; van Diermen et al., 2018). Haq et al. (Haq et al., 2015) included in a meta-analysis 32 studies, with sex as a predictive variable of response, showing no significant differences between women and men. However, as Haq et al. also included studies using sine-wave ECT, results may not be fully generalizable to the current practice. In addition, Van Diermen et al. applied strict selection criteria, leaving out a number of (often large) studies and exclude studies that used ultrabrief-pulse ECT.

Moreover, these studies did not involve sex interaction effects on observed clinical predictors and did not benefit from the advantages of pooling data from a large international consortium.

To investigate how sex differences may affect the effectiveness of ECT treatment in MDD, we analyzed data from multiple sites using the Global ECT-MRI Research Collaboration (GEMRIC) database(Oltedal et al., 2017). Our first aim was to study sex differences in relation to ECT outcome. Our second aim was to study sex differences in common clinical variables associated with ECT outcome.

METHODS

Design

For the purpose of this study, clinical data from GEMRIC was obtained for mega-analysis (i.e., data release version 3.1. DOI 10.17605/OSF.IO/WD436). GEMRIC is a multi-site initiative, pooling clinical and neuroimaging data of ECT patients(Oltedal et al., 2017). For our analyses, we used clinical data concerning patients who received ECT. Informed consent was obtained from all patients according to GEMRIC requirements.

Subjects and assessment

In total, 500 patients fulfilling the ICD-10 criteria for MDD were included from 20 different sites. Classification of depressive episodes was according to ICD-10 diagnosis (i.e., F 32.1 moderate; F32.2 severe without psychotic symptoms; F32.3, severe with psychotic symptoms, F 32.9 depressive episode, unspecified, F34.1 persistent mood disorder). Depression severity was quantified with either 17-item Hamilton Depression Rating Scale (HAM-D)(Hamilton, 1960) or Montgomery-Åsberg Depression Rating Scale (MADRS) (Åsberg et al., 1978) converted to HAM-D as described by Heo et al.(Heo et al., 2007) Remission was defined as a HAM-D score of or below 7 points after ECT. Candidate predictors were selected based on the meta-analyses on remission to ECT .(Haq et al., 2015; van Diermen et al., 2018) Duration of the index episode was defined as the duration of the current depressive episode before treatment with ECT.

Administration of ECT

A detailed description of GEMRIC including site-specific ECT procedures, image acquisition and common data processing methods is available elsewhere (Oltedal et al., 2017). In short, data include patients with a depressive episode who were eligible to receive ECT, typically after failure to respond to conventional psycho- and pharmacotherapy. All included ECT protocols were naturalistic in design, with stimulus parameters not being manipulated for research purposes. ECT practice differed across sites in terms of electrode placement (i.e., right unilateral, bifrontal, and bitemporal), ECT charge and pulse width. Individual need for ECT was clinically determined at each site. The titration method for stimulus dose varied across sites.

Statistical methods

Clinical characteristics and demographics were reported as mean with standard deviation (SD) for continuous variables, while numbers and percentages were computed for categorical variables. To study at baseline differences in clinical characteristics between men and women, differences in

continuous variables were analyzed with independent two-tailed t-tests. Chi-squared tests were used to compare nominal values between men and women. The p-value for significance used for these tests and other tests in our analysis was set at 0.05. We did not apply a correction for multiple statistical testing, such as a Bonferroni correction. The main outcome of our study was measured by response and remission. As these outcomes are small in number and interdependent, we did not apply a correction for multiple comparisons (Schulz and Grimes, 2005). For the additional tests of the clinical characteristics and demographics, the specific individual outcomes are of interest. This advocates against applying a correction in these cases(Armstrong, 2014; Schulz and Grimes, 2005; Streiner and Norman, 2011).

Multivariate logistic regression was performed on candidate predictors to analyze effects, based on log-odds ratios. The dependent variable was remission. Candidate predictors were the following: depression severity at baseline (i.e., HAM-D at baseline), age, duration of index episode, and presence of psychotic symptoms. In addition, we include as a predictor a female dummy variable set equal to 1 for women and to 0 for men.

We considered sex as a moderating variable by interacting all candidate predictors with the female dummy variable and included the interaction terms in the logistic regression analyses (p-value set at 0.10).

Site effects were included as dummy variables for all sites except reference site 'A'. These site effects correct for site-specific characteristics, such as differences in ECT practice. In the logistic regression, we considered sex by interacting all candidate predictors with the female dummy variable. After running the regression with the moderating variables, we determined predictive margins for statistically significant interactions.

Plots of the predictive margins were constructed for these variables. Values were chosen to cover the range of observed outcomes, while maintaining enough observations for each computation. The plots were based on logistic regression with interactions (without site effects) to identify predictive margins sufficiently parsimonious. Data were analyzed using SPSS, version 27 (SPSS Inc., Chicago, IL).

Ethical Issues

All sites contributing data received approval by their local ethical committees or Institutional Review Board. The centralized mega-analysis was approved by the Regional Ethic Committee South-East in Norway (no. 2018/769)(Oltedal et al., 2017).

RESULTS

Demographic and clinical characteristics of the study sample

The baseline sample consisted of 500 severely depressed patients (58.6% women) receiving ECT, who were derived from 20 sites (Table 1) and showed a mean age of 54.8 years (SD 15.4 years). Age, age at onset, family history, and number of previous depressive episodes did not differ between women and men. Women with MDD had significantly higher baseline HAM-D scores (mean 26.4 [SD 7.0]) compared to men (mean 24.4 [SD 7.0], t-test= 3.1, df= 468, p=<0.01); 20.4% of all patients showed presence of psychotic depression, with no significant sex difference in prevalence between women (22.5%) and men (17.4%; $\chi 2=2.0$, df=1, p=0.18). The duration of the index episode was 17.7 months (SD 32.5), showing no significant difference between women (mean 16.4 [SD 33.2]) and men (mean 19.7 [SD 31.4]; t =-0.8, df=240, p= 0.43).

ECT outcome and its possible predictors outcome

The overall remission rate after ECT was 47.0%; 48.0% in women and 45.7% in men ($X^2(1)=0.2$, p=0.70; Table 1).

For depression severity at baseline, longer duration of index episode, and presence of psychotic symptoms no significant associations were found with remission of ECT (p>0.05). Older age was associated with remission in men and women ($\chi 2(1) =18.50$, p=<0.01; see Table 2, Panel A). We observed a significant interaction effect for the duration of the index episode as a sex-specific predictor for remission in women compared to men ($X^2(1)=7.05$, p=0.01; see Table 2, Panels B and C).

The interaction effect showed that for men the likelihood of remission did not vary with the duration of the index episode. In contrast, for women remission was less likely to occur in a longer duration of the index episode (Table 2, Panel B). Other clinical variables (depression severity at baseline [HAM-D at baseline] and presence of psychotic symptoms) did not show statistically significant interaction effects (Table 2, Panel B).

Adding site effects to the logistic regression including sex interactions did not change the result (Table 2, Panel C). Since age was shown to be a predictor for remission in ECT (see panel A), we performed additional analyses estimating a model that also included potential interaction effects with age (next to those with sex). This model, however, did not show statistically significant effects (p-value set at 0.10; data not shown).

Figure 1 shows the predictive margins of duration of index episode for the likelihood of remission to be in line with the findings from the logistic regression, yet with wide and overlapping confidence intervals.

DISCUSSION

This is to, the best of our knowledge, the largest cohort study looking at sex-specific effects on outcome and prediction of outcome of ECT. In this study in 500 patients with MDD, we showed ECT to be equally effective in women and men. Before ECT, depression scores appeared significantly higher in women. Older age was positively associated with reaching remission. Only in women, shorter duration of the index episode proved to be a predictor for remission.

Our sample of patients referred for ECT displayed an equal distribution of sexes, despite the known sex gap in prevalence of depression and manifestation, including help-seeking behavior. This may be because depressive episodes referred for ECT include severe mood symptoms, guilt, suicidal ideation, psychomotor change, and vegetative symptoms also known as melancholic depression (Taylor and Fink, 2006) which may urge clinicians to choose ECT as quick and effective treatment in such conditions. Furthermore, there may be a doctor's delay regarding referral of women, due to their internalizing symptoms. It may also be that sex influences decision-making, as seen in psychotherapy (Hay et al., 2019; Ogrodniczuk, 2006). Although prevalence rates for depression differ in general, this may not hold for melancholic depression(Bogren et al., 2018). We showed ECT to be equally effective in both sexes. This is in line with two smaller studies on patients across psychiatric diagnosis(Bolu et al., 2015; Manohar et al., 2017). Common predictors for remission (i.e., depression severity, duration of index episode, and presence of psychotic symptoms) could not be confirmed in our sample, except for age. All known predictors were equally present in women and men, except for depression severity. In line with previous studies (Cavanagh et al., 2017; Kuehner, 2017; Luppa et al., 2012), women reported higher depression scores. In this study, we investigated sex-interaction effects on clinical variables associated with ECT response, showing no interaction effect of sex with severity of depression, age, or psychotic symptoms. We did observe a significant interaction effect with a shorter duration of index episode to be a sex-specific predictor of remission in women. Adding site effects, which correct for site-specific characteristics such as differences in ECT practice, to the logistic regression including sex interactions did not change the results.

Various factors, on biological, psychological, and social levels, may also contribute to the observed differences in depression between women and men. Biological factors could be hormonal influences (e.g., menopausal state). Psychological factors may involve intrapsychic processes, such as anxiety, lower self-confidence, and ruminative coping with depressed mood. Lastly, social factors, e.g.,

violence and (sexual abuse), may also play a role (Kuehner, 2017). We cannot rule out that these factors, apart from contributing to sex differences in depression, may also influence effectiveness of ECT. Thus, one should always consider confounders that may affect the effectiveness of ECT. In addition, differences in psychiatric comorbidity, physical health burden, and therapy resistance between men and women may influence effectiveness of ECT (Haq et al., 2015; Prudic et al., 2004).

Our findings should not result in unwarranted decreased access to ECT for women. In our opinion it is important that this study will be replicated, with inclusion of other variables influencing treatment outcome (e.g., psychiatric comorbidity). A replication study can address the robustness of the shorter duration of the index episode as a predictor for remission in women, whereas a larger sample may help to show whether the confidence intervals for the corresponding predictive margins are overlapping or not.

Strengths and limitations

GEMRIC is a large and growing international multi-site collaboration with combined clinical and imaging data aiming to determine the mechanisms and predictors of clinical response to ECT. A strength of this study is the naturalistic design, mimicking daily clinical care as closely as possible.

While the multi-site international data may offer a greater generalization of results, this dataset contained missing data on clinical variables which may be associated with response (e.g., psychiatric comorbidity, such as personality disorders, physical health burden, and therapy resistance) (Haq et al., 2015)

This study lends further support to the previously documented observation that patients who undergo prolonged treatment (i.e., have a longer index episode) before ECT are less likely to benefit from ECT. Our finding that this effect applies only to women is new. Women with a longer duration of the index episode may be more likely to experience comorbid psychiatric disorders (e.g., personality disorders or anxiety disorders {Melartin, 2004 #449} which negatively influence the outcome of ECT ((Steinholtz et al., 2021) Furthermore, women in the current sample show a higher percentage of non-melancholic depression with a lower prevalence rate of predictors for a positive ECT outcome (i.e., depressed mood, psychotic symptoms) (Bogren et al., 2018). This may have influenced our results. However, results on the predictive value of melancholic symptoms on ECT efficacy are inconclusive due to heterogeneity of studies (van Diermen et al., 2018).

Future research

As the benefits of ECT depend on the balance between effectiveness and risk of side effects, it is important for clinicians to not only understand sex differences in effectiveness of ECT, but also to have a clear understanding of sex differences in presence of (cognitive) adverse effects. Additional studies identifying the optimal sex-specific ECT settings as well as sex differences in risk of adverse effects are warranted.

CONCLUSION

In the era of precision medicine, additional research should be done to advance individualized treatment recommendations based on biological differences. In this study we considered sex as a variable of interest instead of a confounder in data analysis. The evidence provided by our study suggests that ECT as a biological treatment for depression represents an effective treatment in both sexes, with remission rates independent of sex. In our sample, older age was a predictor of ECT outcome for both sexes and a shorter duration of the index episode was an additional sex-specific predictor for remission in women. For future projects, additional predictors of remission such as comorbid psychiatric disorders and treatment resistance may be examined, thereby also taking adverse effects into account. Future research can also address the robustness of the shorter duration of the index episode as a predictor for remission, where a larger sample could help to show whether the confidence intervals for the corresponding predictive margins are overlapping or not. This study stimulates more sex-specific research and recommendations in clinical guidelines.

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