Psychological Medicine, 2003, **33**, 1473–1477. © 2003 Cambridge University Press
DOI: 10.1017/S0033291703007918 Printed in the United Kingdom

BRIEF COMMUNICATION

Gender differences in response to differing antidepressant drug classes: two negative studies

G. PARKER,[1] K. PARKER, M.-P. AUSTIN, P. MITCHELL AND H. BROTCHIE

From the Mood Disorders Unit, Black Dog Institute and School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

ABSTRACT

Background. A recent US study presented data suggesting that depressed women are more likely to respond to selective serotonin reuptake inhibitor (SSRI) than tricyclic (TCA) antidepressant drug therapies. We have undertaken replication studies in two independent databases.

Method. We have examined for gender differences in SSRI and TCA antidepressant response in both retrospective and prospective naturalistic uncontrolled studies, and in subsets of melancholic and non-melancholic depressed subjects. As the US study had indicated that women under the age of 40 years were particularly likely to show a differential response to SSRIs, we examined for age, gender and interactional effects. In addition, we examined for differential SSRI and TCA responsiveness in a subset of patients who had received drugs from both classes.

Results. We failed to find evidence of women having a preferential response to SSRI medication or, conversely, of men having a superior response to TCA medication. Older age, however, was associated with a superior TCA response and younger age with a superior SSRI response.

Conclusion. As few studies have examined for differential gender and age effects in response to narrow action and broad action antidepressant drugs across major depressive subtypes, gender differential effects remain to be established.

INTRODUCTION

In an intriguing study, Kornstein *et al*. (2000) identified differential gender responses to differing antidepressant drug classes. They studied out-patients with major depression and double depression receiving a 12-week trial of either sertraline (an SSRI) or imipramine (a TCA). Women taking the TCA, and men receiving the SSRI, were more likely to withdraw from the study. Secondly, women were more likely to respond to the SSRI than to the TCA, while the converse held for the men. The TCA response tended to be superior to the SSRI response for men across all age groups, with men also responding significantly faster to the TCA than women. For women over 40 years, the TCA and SSRI responses were comparable while, for females under 40 years, the SSRI response was superior to the TCA response (61% *v*. 40%). The authors speculated that female sex hormones might enhance response to SSRIs or inhibit response to TCAs. They noted that no prior study had examined for sex differences in response to SSRIs.

Thase *et al*. (2000) have previously reviewed the issue of gender differences in response to differing antidepressant treatments. The TCA imipramine showed a superior response rate in men in one meta-analysis (Hamilton *et al*. 1996), the SSRI fluoxetine was no more effective than

[1] Address for correspondence: Professor Gordon Parker, Black Dog Institute, Euroa Unit, Prince of Wales Hospital, High Street, Randwick, Sydney NSW 2031, Australia.

https://doi.org/10.1017/S0033291703007918 Published online by Cambridge University Press

TCAs in one large study of women (Lewis-Hall *et al.* 1997) while, in some 410 dysthymic patients, the SSRI sertraline did not differ in efficacy from the TCA imipramine across the genders. The study by Kornstein *et al.* (2000) is thus particularly intriguing in that gender influenced both TCA and SSRI response.

The inconsistent findings – and the rarity of studies examining for gender differences in antidepressant drug response – encouraged the present analyses. In addition to examining for SSRI/TCA sex differences in both retrospective and prospective studies, the former study allowed us to assess (in a subset of subjects) for gender differences among those who had received both a TCA and an SSRI, a strategy controlling for any individual variation. We also examined age effects, and for any differential effect of melancholic depressive status.

METHOD

As both study procedures have been previously described, only principal features are noted. The retrospective study (Parker *et al.* 1999) involved a clinical panel sample, with psychiatrists assessing their patients' estimate of the effectiveness of all previously received antidepressant drugs. Rating options were: 3 = totally effective; 2 = moderately effective; 1 = somewhat effective; 0 = not effective at all, allowing both dimensional and categorical analyses.

The prospective study (Parker *et al.* 2001*a*) involved one of our unit psychiatrists assessing depressed patients at baseline and 12 months later to establish treatments provided by their managing clinician (whether recommended by our unit psychiatrist or not) and treatment response over that interval. Patients completed Beck state depression (Beck *et al.* 1961) or BDI measures at baseline and at 12 months. At the latter assessment, if the patient judged that a particular drug had been helpful, and the patient had recovered or fully remitted, we rated that treatment as 'effective'. In addition, 'clinical improvement' was assessed by clinician ratings of 1 = more depressed, 2 = no change, 3 = mild improvement, 4 = moderate improvement and 5 = marked improvement or complete remission. Self-reported improvement was operationalized as $\geqslant 20\%$ improvement in BDI score.

The retrospective sample comprised those assessed by one of 27 Australasian psychiatrists and viewed as a representative sample of depressed out-patients, while the prospective sample was weighted to the more severe and treatment resistant disorders. In both studies DSM-IV decision rules were applied to distinguish those with melancholic and non-melancholic depression.

As Kornstein *et al.* (2000) established an age differential effect for SSRI and TCA response in women using an age cut-off of 40 years, we examined any such age effect. Lacking data on menopausal status, we also examined an age cut-off of 50 years.

RESULTS

The retrospective study

The sample comprised 346 non-psychotically depressed patients, with 106 (30·6%) meeting DSM-IV-defined melancholia criteria. The males were older than the females (respective means of 47·9 and 43·1, $t = 2{\cdot}8$, df = 344, $P < 0{\cdot}01$), while 210 (60·7%) had previously received a TCA and 219 (63·3%) an SSRI. Table 1 details that, in the total sample, the genders did not differ in the rates of reporting either a TCA or an SSRI as 'effective' (i.e. totally or moderately effective compared to residual categories). For the melancholic subsample, there were no differences in judging TCAs as effective, being 9/23 (39·1%) for males and 15/39 (38·5%) for females, or in judging SSRIs as effective, being 9/29 (31·0%) for males and 9/45 (20·0%) for females. For the non-melancholic subsample, females (44/105, 41·9%) were more likely ($\chi^2 = 4{\cdot}6$, $P < 0{\cdot}05$) than males to report a TCA as effective, but females (34/98, 34·7%) did not differ from males (15/47, 31·9%) in reporting an SSRI as effective.

Any impact of an age cut-off of 40 years was examined. Examining women and men together, while TCA effectiveness did not differ by age group ($F = 0{\cdot}3$), SSRI effectiveness was higher in the younger age group ($F = 4{\cdot}5$, $P = 0{\cdot}03$). No gender effect was evident, however, in regard to TCA ($F = 1{\cdot}4$, NS) or SSRI ($F = 0{\cdot}1$, NS) effectiveness, nor any age group by gender interaction evident for TCA ($F = 0{\cdot}4$) or SSRI ($F = 2{\cdot}1$) effectiveness. When the age cut-off was raised to 50 years, a different pattern emerged. TCA effectiveness was higher in men and

https://doi.org/10.1017/S0033291703007918 Published online by Cambridge University Press

Table 1. *Comparison of responses to TCAs and SSRIs by males and females in two samples*

	Males		Females		
Sample and drug	*n*/*N*	(%)	*n*/*N*	(%)	χ^2
Retrospective					
TCA effectiveness*	19/66	(28·8)	59/144	(41·0)	2·9
SSRI effectiveness*	24/76	(31·6)	43/143	(30·1)	0·1
Prospective					
TCA effective†	7/20	(35·0)	13/38	(34·2)	0·0
SSRI effective†	7/31	(22·6)	13/38	(34·2)	1·1
TCA clinically improved‡	10/20	(50·0)	17/38	(44·7)	0·3
SSRI clinically improved‡	9/30	(30·0)	18/36	(50·0)	2·7
TCA self-report improved§	8/19	(42·1)	9/31	(29·0)	0·9
SSRI self-report improved§	6/30	(20·0)	8/27	(29·6)	0·7

* Psychiatrist-assessed as totally or moderately effective.
† Patient judged the drug as helpful and had recovered or fully remitted.
‡ Clinician rated the patient as moderately improved or remitted.
§ Improvement ⩾ by 20% on Beck Depression Inventory scores from follow-up to baseline.

women over 50 years ($F=10·3$, $P<0·002$). However, SSRI effectiveness did not differ by age group ($F=0·6$), neither was there any age group by gender interaction for TCA ($F=0·01$) or SSRI ($F=0·1$) effectiveness.

In the whole sample, 39·7% (50/127) of the males and 51·1% (112/219) of the females had received both a TCA and an SSRI at some stage. Analysing effectiveness scores (i.e. 0–3) quantitatively, we established similar TCA *v.* SSRI scores for males (0·84 *v.* 0·80) and for females (1·04 *v.* 0·85), with analysis of variance tests establishing that there was no overall TCA *v.* SSRI difference ($F=1·6$), no gender difference ($F=0·9$) and no drug class/gender interaction effect ($F=0·7$).

The prospective study

The sample comprised 162 non-psychotically depressed subjects, with 55 (34%) meeting DSM-IV criteria for a current melancholic episode. There was no age difference between the males and females (43·2 *v.* 43·4, $t=0·10$, df = 160, $P=0·92$). Over the next 12 months, 58 (35·8%) received a TCA and 69 (42·6%) an SSRI. Table 1 data indicate that, at the 12-month follow-up, the genders did not differ (either in response to receiving a TCA or an SSRI) in terms of that treatment being rated as 'effective', in terms of being assessed as clinically improved, or in terms of improvement quantified by the Beck self-report measure, although there were non-significant trends for the females to have superior SSRI responses. Supplementary analyses of those with melancholic or non-melancholic depression failed to identify any significant differences, although cell sizes were small.

The sample was similarly subdivided into those aged ⩽40 and a residual older group. Log-linear analyses contrasting treatment (TCA *v.* SSRI) by sex and by age group produced no significant differences within the whole group or in the sub-sets of melancholic and non-melancholic subgroups. Analyses using a cut-off of 50 years were also non-significant.

DISCUSSION

No gender differences in TCA and SSRI response in non-psychotically depressed patients were identified in the prospective study. In the retrospective study, females in the non-melancholic subset were more likely than males to report a TCA as having been effective. More importantly, we identified differing patterns for TCA and SSRI effectiveness for both sexes when differing age cut-offs were examined in the combined melancholic and non-melancholic sample. Using an age cut-off of 40 years, SSRIs appeared more effective in the younger group, while using a cut-off of 50 years, TCAs were more effective in the older group. These results are most parsimoniously explained by a more general phenomenon of TCAs being more effective in older subjects and SSRIs in younger subjects, so that raising the age cut-off to 50 years diffused the suggested benefit of SSRIs to subjects younger than 40 while it consolidated the greater effectiveness of TCAs to older subjects.

However, we failed to find any significant gender effects, or any interaction of gender and age group (whether the cut-off was 40 or 50 years) on TCA or SSRI effectiveness. In an earlier sample analysis, Parker (2002) identified SSRI effectiveness decreasing with age in those with melancholic depression, and no impact of age or depressive subtype on TCA response, postulating that, as those with melancholia age, response to a narrow action antidepressant (such as an SSRI) is reduced. As our current analyses identified an age effect (that did not differentiate by gender) on TCA and SSRI effectiveness, we

https://doi.org/10.1017/S0033291703007918 Published online by Cambridge University Press

again suspect an effect of age on the phenotypic presentation of depression (Parker *et al.* 2001*b*) rather than a gender effect. Perhaps even more importantly, we failed to determine any differential response by gender for subjects who had received both an SSRI and a TCA.

Our failure to identify a gender difference could reflect limitations to our 'clinical effectiveness' studies – being non-randomized and not placebo-controlled, they lacked the rigour of formalized studies. Our assessments relied considerably on patients' recall of antidepressant effectiveness, and involved lengthy periods of assessment (i.e. lifetime exposure in the retrospective study and 12-month outcome in the prospective study) rather than short-term intervals. Other limitations lay in not determining how long patients had been trialled on the differing antidepressants, or in establishing whether such medications had been ceased because of side-effects, while datasets were not large enough to preclude Type II errors. Furthermore, our data on age referred to age at assessment rather than when subjects had actually received their antidepressant drugs.

Conversely, could results from the Kornstein *et al.* (2000) study be idiosyncratic? Examining their detailed and comprehensive report, few alternate explanations occur to us. Their study design allowed the antidepressant drugs to be titrated upwards depending on clinical response and side-effects. At endpoint the mean sertraline dose was 139·6 mg/day for women and 143·2 mg/day for men, while the mean imipramine dose was 196·3 mg/day for women and 207·4 mg/day for men. Such high tricyclic doses, particularly for women, could suggest that women would be more likely to experience TCA-induced side-effects, and so withdraw from the study and thus be less likely to 'respond'. Those authors provide several arguments to rebut an overall 'tolerability' explanation. Secondly, and as conceded by the authors, any role of oral contraceptives and hormone replacement therapy remains to be examined in future studies. Thirdly, the women in their study were significantly younger than their men and, as data indicate SSRIs as more effective in younger subjects, their results may have reflected an age contribution.

Earlier we noted the review by Thase *et al.* (2000) indicating quite variable results in three previous studies – one indicating a superior result to TCAs in males and two studies failing to identify any gender difference, suggesting that more reported studies have been negative rather than positive. In a further recent study, Quitkin *et al.* (2002) analysed datasets involving 1746 patients treated in controlled studies of antidepressants – failing to find any gender or age difference effects on differential TCA or SSRI response rates.

The possibility that gender, age and even menopausal status may influence response to differing antidepressant classes is an issue of deceptive importance. It will not be resolved by results from any one individual study. As the pharmaceutical industry possesses many large datasets, analyses of their databases (and particularly efficacy studies contrasting drugs of differing classes) together with clinical effectiveness studies would assist pursuit of any such phenomenon. Clarification is important in light of the major clinical implications.

This study was supported by an NHMRC Program Grant (993208) and an Infrastructure Grant from the Department of Health. We thank Kerrie Eyers for manuscript assistance.

REFERENCES

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J. E. & Ersbaugh, J. K. (1961). An inventory for measuring depression. *Archives of General Psychiatry* **4**, 561–571.

Hamilton, J. A., Grant, M. & Jensvold, M. F. (1996). Sex and treatment of depression. In *Psychopharmacology and Women. Sex, Gender and Hormones* (ed. M. F. Jensvold, U. Halbreich and J. A. Hamilton), pp. 241–260. American Psychiatric Association: Washington, DC.

Lewis-Hall, F. C., Wilson, M. G., Tepner, R. G. & Koke, S. C. (1997). Fluoxetine vs. tricyclic antidepressant in women with major depressive disorder. *Journal of Womens Health* **6**, 337–343.

Kornstein, S. G., Schatzberg, A. F., Thase, M. E., Yonkers, K. A., McCullough, J. P., Keitner, G. I., Gelenberg, A. J., Davis, S. M., Harrison, W. M. & Keller, M. B. (2000). Gender differences in treatment response to sertraline versus imipramine in chronic depression. *American Journal of Psychiatry* **157**, 1445–1452.

Parker, G. (2002). Differential effectiveness of new and older antidepressants appears mediated by age effect on the phenotypic expression of depression. *Acta Psychiatrica Scandinavica* **106**, 168–170.

Parker, G., Mitchell, P., Wilhelm, K., Menkes, D., Snowdon, J., Schweitzer, I., Grounds, D., Skerritt, P., Roy, K. & Hadzi-Pavlovic, D. (1999). Are the newer antidepressant drugs as effective as established physical treatments? Results from an Australian clinical panel study. *Australian and New Zealand Journal of Psychiatry* **33**, 874–881.

Parker, G., Roy, K., Wilhelm, K. & Mitchell, P. (2001*a*). Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *Journal of Clinical Psychiatry* **62**, 117–125.

https://doi.org/10.1017/S0033291703007918 Published online by Cambridge University Press

Parker, G., Hadzi-Pavlovic, D., Wilhelm, K. & Mitchell, P. (2001*b*). The differential impact of age on the phenomenology of melancholia. *Psychological Medicine* **31**, 1231–1236.

Quitkin, F. M., Stewart, J. W., McGrath, P. J., Taylor, B. P., Tisminetzky, M. S., Petkova, E., Chen, Y., Ma, G. & Klein, D. F. (2002). Are there differences between women's and men's antidepressant responses? *American Journal of Psychiatry* **159**, 1848–1854.

Thase, M. E., Frank, E., Kornstein, S. G. & Yonkers, K. A. (2000). Gender differences in response to treatments of depression. In *Gender and Its Effects on Psychopathology* (ed. E. Frank), pp. 103–129. American Psychiatric Press: Washington, DC.

https://doi.org/10.1017/S0033291703007918 Published online by Cambridge University Press