

Research report

Treatment received by depressed patients in Japan and its determinants: naturalistic observation from a multi-center collaborative follow-up study

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Abstract

Background: Undertreatment of depression appears widespread but the available literature is limited to North American and European countries. We aimed to examine the treatment received by patients with major depression in Japan and to elucidate any predictor of their treatment level. **Methods:** A naturalistic, prospective follow-up study of an inception cohort of subjects with mood disorders was undertaken in psychiatric departments of 13 university hospitals, those of six general hospitals, three mental hospitals and one community mental health center from all over Japan. A total of 95 patients without any prior antidepressant treatment were diagnosed with major depression according to DSM-IV and were followed up every month until treatment termination and every 6 months thereafter. **Results:** The follow-up information was available in 98 to 97% of the cohort. The proportion of patients receiving less than 125 mg/day of imipramine or equivalent reached 69% (95% CI: 58–78%) at 1 month and 67% (95% CI: 54–77%) at 6 months. A few clinical variables were significantly associated with inadequate antidepressant prescription but altogether they explained only 5 to 14% of the variance observed. **Conclusions:** Japan was no exception to the other industrialized countries in its less than optimal provision of treatment to major depression and its lack of explanatory predictors for this common practice. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Major depression; Follow-up study; Antidepressive agents; Benzodiazepines

1. Introduction

Undertreatment of depression appears to be ubiquitous. In the United States, among those with major depression treated in the community before

they visited the university hospitals participating in the NIMH Collaborative Program on the Psychobiology of Depression, only 12% had received greater than 150 mg of imipramine or its equivalent (Keller et al., 1982). In the subsequent treatment of these patients in these leading academic institutions, 31% of the in-patients received either no or very low antidepressant somatotherapy, and only 49% received at least 200 mg of imipramine or its equivalent.

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lent for 4 consecutive weeks; among the out-patients, 53% were in the former category and only 19% were in the latter category (Keller et al., 1986). The Medical Outcomes Study has shown that only 16% of depressed out-patients visiting general medical clinicians and 34% of such patients visiting psychiatrists received some antidepressant medication, and that among those receiving some antidepressant medication, 39% used a subtherapeutic daily dose (Wells et al., 1994). The recent consensus statement organized by the National Depressive and Manic-Depressive Association had to conclude that 'there is overwhelming evidence that individuals with depression are being seriously undertreated' (Hirschfeld et al., 1997).

In the United Kingdom, the situation appears to be no different. It was pointed out early on in a survey of general practitioners that only 27% of those treated with a tricyclic antidepressant received adequate dosage (Johnson, 1974). More recent studies reported no change. As many as 88% of prescriptions for tricyclic antidepressants are prescribed by general practitioners at doses below those recommended by the consensus guidelines (Donoghue and Tylee, 1996). Even at the Maudsley Hospital, only 36% of the patients on antidepressants were on therapeutic dosage; among those who did not remit after 4 months of treatment, the proportion of patients receiving an inadequate dosage reached 78% (Brugha and Bebbington, 1992).

Similar data are reported from other European countries. A prescription database analysis in Denmark showed that the estimated daily doses for the tricyclic antidepressants were generally low, the third quartile being less than 100 mg (Rosholm et al., 1993). The elderly in-patients in Dutch psychiatric hospitals, when diagnosed with major depression, were mostly able to receive an antidepressant but adequate dosage was achieved in only 45% of them (Heeren et al., 1997).

A corollary of undertreatment of depression is its 'overtreatment' by benzodiazepines, whose effectiveness against depression has been generally shown, except possibly for triazolo-benzodiazepines, to be inferior to standard antidepressants (Birkenhager et al., 1995). As a matter of fact, benzodiazepines may be more often prescribed than antidepressants for depression. For example, among those with major

depression treated in the community before visiting university hospitals, 34% received some antidepressants while 55% received some minor tranquilizers (Keller et al., 1982). According to the Medical Outcomes Study (Wells et al., 1994), 35% of the depressed patients seen by psychiatrists received minor tranquilizers (in contrast to 34% receiving antidepressants) and 20% of those seen by general medical clinicians received the former (in contrast to 16% receiving the latter).

Are there any clinical features that interfere with these patients' receiving optimal care? Several papers have addressed this enigma. Keller et al. (1982) analyzed the association between demographic and clinical variables and the adequacy of antidepressant treatment given to the patients before visiting university hospitals. Inadequate therapy was associated with younger age, and shorter duration, less severity and the absence of anxiety of the index depressive episode; but, taken together, these variables accounted for a small fraction of the variance (18%) in the treatment received. In the subsequent treatment of these depressed patients at these university centers, again only a few clinical factors were found to be predictive of treatment intensity but very large differences in the amount and type of treatment were noted across the five centers (Keller et al., 1986).

None of these studies of 'standard' clinical practices for major depression have been conducted outside the North American-European countries. Could it be different and indeed better in some places in the world? The Group for Longitudinal Affective Disorders Study (GLADS) in Japan has been conducting a multi-center prospective follow-up study of a broad spectrum of affective disorders (Furukawa et al., 1995). The present paper aims to report the treatment received by depressed patients in Japan and its predictors.

2. Methods

2.1. Subjects and procedures

The Intensive Prospective Study of the GLADS Project aims at detailed assessment of a limited number of patients with broadly defined affective disorders. The 23 hospitals collaborating in this

study include psychiatric departments of 13 university hospitals, those of six general hospitals, three mental hospitals and one community mental health center from all over Japan. Each hospital examined a representative subset of its first-visit patients according to the predetermined rules, the details of which were left to individual centers as time and human resources varied in each center.

These first-visit patients were first interviewed by a psychiatrist using a semi-structured interview called the Psychiatric Initial Screening for Affective disorders (PISA) (Kitamura, 1992). Based on these data, each participating center entered the first patient that satisfied the following criteria either every month or every 2 months in order to avoid a seasonal imbalance. The inclusion criteria for the Intensive Prospective Study were: (1) depressive state defined as presenting with depressed mood or anhedonia lasting longer than 4 days, or manic state defined as presenting with elated, expansive or irritable mood lasting longer than 4 days; (2) having received no antidepressant or antipsychotic medication in the preceding 3 months; and (3) aged 18 or older. Excluded were subjects who suffered from conditions such as mental retardation, dementia or hearing disability which would render detailed psychopathological and psychosocial assessment difficult. The selected subjects were then given detailed information concerning the study protocol and only those patients who gave their written informed consent were finally included in the study. The patients eligible for and consenting to the study were then interviewed within 1 week from entry by a psychiatrist using a semi-structured interview called the Comprehensive Assessment List for Affective disorders (COALA), Entry version (Furukawa, 1992).

The GLADS Project is a naturalistic follow-up study and there was no control over the treatment in its protocol.

2.2. Instruments

The PISA is the screening instrument for the first-visit patients representative of the participating centers. The COALA consists of a series of semi-structured interviews which enable serial assessment of the cohort; these include the entry version,

monthly follow-up version and 6-monthly follow-up version. Elsewhere we have explained their contents in details and reported their reliability to be satisfactory to excellent (Furukawa et al., 1995). The COALA includes the Global Assessment Scale (GAS), and the score for the 17-item Hamilton Rating Scale for Depression (HRSD) can be calculated directly from the COALA variables. The information about the treatment upon the first visit, after 1 month of treatment and after 6 months of treatment was gathered at the time of the 6-month follow-up.

2.3. Analyses

The equivalence of antidepressants was calculated, in accordance with the advice of WHO (Tansella and Micciolo, 1992), as follows by equating the average daily dosage of the preparation recommended for its main indication in adults. When the standard maximum daily dosage fell within 150 and 200 mg/day, such drugs were considered equivalent. They included, for example, classical tricyclic antidepressants. When the maximum daily dosage was below 150 mg/day, the milligram was multiplied accordingly. These drugs included maprotiline (the maximum daily dosage was 75 mg and so the prescribed milligram was doubled to reach the equivalence), mianserine (the maximum daily dosage was 60 mg and the prescribed dosage was tripled), setiptiline (the maximum daily dosage was 6 mg and the prescribed dosage was multiplied by 30) and safrazine (the maximum daily dosage was 30 mg/day and the prescribed dosage was multiplied by five). At the time of the present study, no selective serotonin-reuptake inhibitor (SSRI) was marketed in Japan.

In order to determine adequacy of antidepressant dosage, we followed the consensus guidelines published by the Royal College of Psychiatrists and the Royal College of General Practitioners and consider imipramine or its equivalent less than 125 mg/day as no more effective than placebo (Paykel and Priest, 1992). We set as our main outcome measures the percentage of patients receiving this adequate dosage at 1 and 6 months of follow-up because it is usually difficult to dispense the optimum amount of antidepressant from the beginning and because many guidelines (Paykel and Priest, 1992; Depression

Guideline Panel, 1993) recommend that continuation therapy be given at full therapeutic dosage for at least 6 months after clinical remission.

We used the statistical package SPSS for Windows 8.0 (SPSS Inc, 1997). Fisher exact tests or chi-square tests were used for categorical variables and Mann–Whitney *U* or Kruskal–Wallis tests for continuous variables. All the tests of significance are two-tailed. Given the many variables examined, we defined statistical significance at or below 0.01 and reported any findings between 0.01 and 0.05 as suggestive.

3. Results

During the period between December 1992 and December 1995, 1968 patients were screened at the 23 participating centers. Out of these, 126 patients, selected according to pre-specified rules to avoid seasonal imbalance and giving their written informed consent, were formally entered into the study and are now being followed up at the collaborating centers. The 126 patients were not different from the rest of the larger pool of patients ($n = 916$) who satisfied the eligibility criteria but were not entered into the study in terms of age ($t = -0.59$, $df = 1014$, $P = 0.56$), sex ($\chi^2 = 0.58$, $df = 1$, $P = 0.81$) or season of entry ($\chi^2 = 1.90$, $df = 3$, $P = 0.59$).

The diagnoses of these 126 subjects according to DSM-IV were major depressive disorder ($n = 95$), depressive disorder NOS (15), bipolar I disorder (7), bipolar II disorder (3) and others (6). In the following analyses, we will concentrate on the 95 subjects who were diagnosed with major depressive disorder according to DSM-IV (single episode, 67; recurrent, 28). Nine had other axis I comorbid disorders: panic disorder (3), generalized anxiety disorder (2), social phobia (1), anorexia nervosa (1), alcohol intoxication (1) and vascular dementia (1). Fourteen of them

(15%) were in-patients at the time of the administration of the COALA Entry version.

Of these 95 patients with major depressive disorder, information regarding the treatment received at entry, at 1 month and at 6 months was available for 95 (100%), 93 (98%) and 92 (97%), respectively. Out of those for whom such information was available, 94 (99%) received at least some medication at the time of their first consultation, 85 (91%) at 1-month follow-up and 58 (63%) at 6-month follow-up. The classes of medications prescribed to those who received at least one medication at each of the three time periods are tabulated in Table 1. Approximately 80% of the patients received some antidepressants upon entry, at 1 month and at 6 months. Excluding those used as hypnotics, one in two patients was prescribed benzodiazepine anxiolytics. No patient was treated with electroconvulsive therapy or any specialized form of psychotherapy such as Interpersonal Psychotherapy or Cognitive-Behavior Therapy.

We first examined the amount of antidepressants prescribed. Among the patients receiving at least one medication, the average \pm S.D. amount of antidepressants in imipramine equivalents as defined in Section 2 was 60 ± 44 mg (range: 0 to 200 mg) per day upon entry, 85 ± 73 mg (range: 0 to 300 mg) per day at 1 month, and 86 ± 81 mg (range: 0 to 400 mg) per day at 6 months. Among the patients receiving at least one medication, those who received less than 125 mg/day of imipramine equivalents reached 69% (95% CI: 58 to 78%) at 1 month and 67% (95% CI: 54 to 77%) at 6 months.

We next studied which type of patients were less likely to receive adequate antidepressant treatment. The variables examined include the demographic ones of sex, age, education and marital status; course features such as length of the present episode; symptomatological ones of comorbidity, endogenei-

Table 1
Medications prescribed for patients with major depressive disorder in Japan^a

	Antidepressants	Benzodiazepine anxiolytics	Antipsychotics	Lithium
Upon entry ($n = 94$)	81%	60%	11%	5%
At 1 month ($n = 85$)	82%	53%	14%	6%
At 6 months ($n = 58$)	81%	48%	12%	12%

^a The denominator is the number of patients receiving at least one medication at each time period.

ty, psychotic features, and severity of depression as measured by the HRSD; and global function as measured with the GAS before and during the episode. All these variables, except for HRSD and GAS scores during follow-up, were evaluated at baseline. At 1 month, there was a trend for the patients receiving less than 125 mg of imipramine equivalent per day to have a lower HRSD score than those receiving 125 mg or more (9.8 ± 8.5 vs. 13.0 ± 7.0 ; Mann–Whitney $U = 435.5$, $P = 0.045$); no other variable could predict the adequacy of antidepressant treatment at 1 month. At 6 months, the HRSD score or any other variable could not predict the adequacy of antidepressant prescription; there was again a trend, however, for the former to show lower HRSD scores at 1 through 5 months of follow-up than the latter (for example, 4.2 ± 6.5 vs. 8.5 ± 7.6 ; Mann–Whitney $U = 121.5$, $P = 0.032$ for HRSD at 5 months). Entering all these trend variables into a logistic regression, these predictors were able to explain 5% of variance in the treatment adequacy at 1 month and 14% at 6 months.

We classified the treatment settings into three types (university hospitals, general hospitals and mental hospitals) and examined whether there was any difference in the amount of antidepressant prescribed among treatment settings. Both at 1 and 6 months, psychiatrists working in university hospitals tended to prescribe a smaller amount of antidepressants than their colleagues working in other settings (Kruskal–Wallis $\chi^2 = 6.64$, $df = 2$, $P = 0.036$ at 1 month, and $\chi^2 = 6.67$, $df = 2$, $P = 0.036$ at 6 months), although post hoc pairwise comparisons revealed only one statistically significant difference between university psychiatrists and general hospital psychiatrists at 1 month (70.7 ± 71.9 mg vs. 111.4 ± 74.3 mg; Mann–Whitney $U = 371.5$, $P = 0.017$).

We also analyzed the predictors of the concomitant use of benzodiazepine anxiolytics. The severity of psychic and somatic anxiety as measured by the corresponding items of the COALA were examined in addition to the various variables listed above. Those who were prescribed a benzodiazepine in addition to an antidepressant from the beginning were significantly younger (41.4 ± 13.6 vs. 51.7 ± 13.2 ; Mann–Whitney $U = 407.5$, $P = 0.002$), were more severely depressed (HRSD score of

22.3 ± 8.5 vs. 17.5 ± 7.8 ; Mann–Whitney $U = 431$, $P = 0.005$), and had poorer global functioning (GAS score of 48.8 ± 9.8 vs. 55.6 ± 13.2 ; Mann–Whitney $U = 442$, $P = 0.007$) than those who were prescribed an antidepressant only. Altogether these variables explained 32% of the variance whether to add a benzodiazepine anxiolytic to an antidepressant. The site differences were unable to explain the percentage of benzodiazepine prescription.

4. Discussion

The strengths of the present study include the representativeness of the sample and the prospective, serial collection of data on an inception cohort of subjects diagnosed with major depression through a reliable semi-structured interview. Although the 23 participating centers of the IPS arm of the GLADS Project were not a random selection from all the psychiatric institutions in Japan but should rather be considered as ones with interest in and motivation for treatment of mood disorders, they consist of various types of institutions from all over Japan, and within each facility the selected sample was representative of the eligible first-visit patients during the study period. The obtained results should therefore be more generalizable to Japanese psychiatric patients in general than, for example, a study from a group of university hospitals or from one mental hospital. Although ours is not the first prospective study on ‘standard’ clinical practices for depression, it should be noted that of the number of studies reviewed in Section 1, only two groups of investigators, namely those at the five university centers of the NIMH Collaborative Program on the Psychobiology of Depression (Keller et al., 1982, 1986) and at the Maudsley Hospital (Brugha and Bebbington, 1992), had employed the prospective cohort method. These studies were able to minimize the weaknesses inherent in retrospective studies such as recall bias, missing data and inconsistent application of decision criteria. Neither cohort of these two groups, however, can be said to be representative of their respective country. Moreover in many of the existing studies in the literature, especially those using large national prescription databases, the diagnosis of major depression is open to some uncertainty.

The weaknesses of the present study include the small number of patients actually entered and followed-up and our failure to collect information regarding several important factors in determining the adequacy of antidepressant treatment, including duration of antidepressant prescription, emergence of side effects, physician differences in their psychiatric training and clinical philosophy, and the patient preferences. In all likelihood, though, if we take the duration of antidepressant prescription into account as did some but not all of the foregoing studies, the proportion of patients receiving adequate antidepressant treatment would be even lower. Moreover, no SSRI was marketed in Japan at the time of the present survey. It is reported that the introduction of SSRIs has resulted in the increase in the proportion of patients with major depression receiving at least some antidepressant at American psychiatrists from 40% to 61% (Pincus et al., 1998) and in the proportion of adequate antidepressant prescription among British general practitioners from 41% to 53% (Donoghue et al., 1996). However, these two surveys also show that the absolute number of tricyclic antidepressant prescriptions has slightly increased and there is no sign of amelioration in the rate of the prescriptions at the so-called adequate dosage for them (Donoghue et al., 1996; Pincus et al., 1998).

With these caveats in mind, the findings of the present study can be summarized as follows. Firstly, we confirmed that Japan was no exception to the other industrialized countries in its provision of treatment to major depression. Although the majority of the patients diagnosed with major depression were administered some antidepressant, its dosage was very often below the recommended effective range even 1 to 6 months after commencement of the treatment.

Secondly, our study also confirmed the lack of predictors for the antidepressant therapy received by depressed patients. Although those with more symptoms of depression tended to receive a greater amount of antidepressant, this could explain only a small percentage of the variance in the adequacy of antidepressant treatment at either 1 or 6 months of follow-up.

In Japan polypharmacy appeared to be an overwhelming rule rather than an occasional exception

from the very beginning of the treatment. Benzodiazepines were very frequently prescribed for major depression, especially in combination with an antidepressant. Benzodiazepine-antidepressant combination therapy has been shown to be superior to an antidepressant alone in the initial few weeks of treatment in some RCTs but not in others (Feet et al., 1985; Smith et al., 1998); there is no RCT to show the benefit of the former beyond this period and one RCT to demonstrate that withdrawing the additional benzodiazepine can worsen the depression (Feet et al., 1988). The factors influencing the Japanese clinicians' decision to add an anxiolytic benzodiazepine to an antidepressant were found to include the age of the subject, severity of depression and of global functioning impairment and the patient's personality traits but not the level of anxiety per se. Apparently these practices have no ground in the currently available best evidence.

Coupled with the problems of the low consultation rates of the depressives in the community and the low recognition rates of those who visit doctors, we wonder if there ever will be a time when, in a fictitious conversation between an epidemiologist and a psychiatrist (Brugha, 1995), the latter can answer proudly to the former's question 'How much has the prevalence of depression fallen since its effective treatments became widely available?'

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References

- Birkenhager, T.K., Moleman, P., Nolen, W.A., 1995. Benzodiazepines for depression? A review of the literature. *Int. Clin. Psychopharmacol.* 10, 181–195.
- Brugha, T.S., 1995. Depression undertreatment: lost cohorts, lost opportunities? *Psychol. Med.* 25, 3–6.
- Brugha, T.S., Bebbington, P.E., 1992. The undertreatment of

- depression. *Eur. Arch. Psychiatry Clin. Neurosci.* 242, 103–108.
- Depression Guideline Panel, 1993. *Clinical Practice Guideline: Depression in Primary Care 2: Treatment of Major Depression*. US Department of Health and Human Services, Agency for Health Care Policy and Research, Rockville, MD, AHCPR Publication 93-0551.
- Donoghue, J.M., Tylee, A., 1996. The treatment of depression: prescribing patterns of antidepressants in primary care in the UK. *Br. J. Psychiatry* 168, 164–168.
- Donoghue, J., Tylee, A., Wildgust, H., 1996. Cross sectional database analysis of antidepressant prescribing in general practice in the United Kingdom, 1993–5. *Br. Med. J.* 313, 861–862.
- Feet, P.O., Larsen, S., Robak, O.H., 1985. A double blind study in out-patients with primary non-agitated depression treated with imipramine in combination with placebo, diazepam or dextroamphetamine. *Acta Psychiatr. Scand.* 72, 334–340.
- Feet, P.O., Larsen, S., Lillevold, P.E., Robak, O.H., 1988. Withdrawal reactions to diazepam in combined imipramine/diazepam treatment of primary nonagitated depressed outpatients. *Acta Psychiatr. Scand.* 78, 341–347.
- Furukawa, T., 1992. *Comprehensive Assessment List for Affective disorders (COALA)*. National Institute of Mental Health, National Center for Neurology and Psychiatry, Ichikawa, In Japanese.
- Furukawa, T., Takahashi, K., Kitamura, T., Okawa, M., Miyaoka, H., Hirai, T., Ueda, H., Sakamoto, K., Miki, K., Fujita, K., Anraku, K., Yokouchi, T., Mizukawa, R., Hirano, M., Iida, S., Yoshimura, R., Kamei, K., Tsuboi, K., Yoneda, H., Ban, T.A., 1995. The Comprehensive Assessment List for Affective Disorders (COALA): a polydiagnostic, comprehensive, and serial semistructured interview system for affective and related disorders. *Acta Psychiatr. Scand. Suppl.* 387, 1–36.
- Heeren, T.J., Derksen, P., von Heycop Ten Ham, B.F., van Gent, P.P.J., 1997. Treatment, outcome and predictors of response in elderly depressed in-patients. *Br. J. Psychiatry* 170, 436–440.
- Hirschfeld, R.M., Keller, M.B., Panico, S., Arons, B.S., Barlow, D., Davidoff, F., Endicott, J., Froom, J., Goldstein, M., Gorman, J.M., Marek, R.G., Maurer, T.A., Meyer, R., Phillips, K., Ross, J., Schwenk, T.L., Sharfstein, S.S., Thase, M.E., Wyatt, R.J., 1997. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression [see comments]. *J. Am. Med. Assoc.* 277, 333–340.
- Johnson, D.A.W., 1974. A study of the use of antidepressant medication in general practice. *Br. J. Psychiatry* 125, 186–192.
- Keller, M.B., Klerman, G.L., Lavori, P.W., Fawcett, J.A., Coryell, W., Endicott, J., 1982. Treatment received by depressed patients. *J. Am. Med. Assoc.* 248, 1848–1855.
- Keller, M.B., Lavori, P.W., Klerman, G.L., Andreasen, N.C., Endicott, J., Coryell, W., Fawcett, J., Rice, J.P., Hirschfeld, R.M.A., 1986. Low levels and lack of predictors of somatotherapy and psychotherapy received by depressed patients. *Arch. Gen. Psychiatry* 43, 458–466.
- Kitamura, T., 1992. *Psychiatric Initial Screening for Affective disorders (PISA)*. National Institute of Mental Health, National Center for Neurology and Psychiatry, Ichikawa, In Japanese.
- Paykel, E.S., Priest, R.G., 1992. Recognition and management of depression in general practice: consensus statement. *Br. Med. J.* 305, 1198–1202.
- Pincus, H.A., Tanielian, T.L., Marcus, S.C., Olfson, M., Zarin, D.A., Thompson, J., Zito, J.M., 1998. Prescribing trends in psychotropic medications: primary care, psychiatry, and other medical specialties. *J. Am. Med. Assoc.* 279, 526–531.
- Rosholm, J.-U., Hallas, J., Gram, L.F., 1993. Outpatient utilization of antidepressants: a prescription database analysis. *J. Affect. Disord.* 27, 21–28.
- Smith, W.T., Lønborg, P.D., Glaudin, V., Painter, J.R., 1998. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am. J. Psychiatry* 155, 1339–1345.
- SPSS Inc, 1997. *SPSS for Windows Version 8.0*. SPSS Inc, Chicago.
- Tansella, M., Micciolo, R., 1992. Trends in the prescription of antidepressants in urban and rural general practices. *J. Affect. Disord.* 24, 117–125.
- Wells, K.B., Katon, W., Rogers, B., Camp, P., 1994. Use of minor tranquilizers and antidepressant medications by depressed outpatients: results from the Medical Outcomes Study. *Am. J. Psychiatry* 151, 694–700.