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Treatment of Depressive Disorders with and without Medication – A Naturalistic Study

Objective: Although randomized clinical trials are the standard method for comparing the efficacy of various depression treatments, the external validity and generalizability of findings obtained by this approach can be questioned for several reasons. In this naturalistic study, we compared the effectiveness of treatments conducted by psychiatrists and clinical psychologists without prescription of drugs to treatments by psychiatrists and physicians using antidepressant agents in patients with depressive disorders in a representative sample of the normal population. Our assumption was that this sample is more representative for subjects treated for depressive disorders than subjects included in controlled trials. **Methods:** In a *post hoc* analysis, the health status of depressed patients under treatment for major, minor or recurrent brief depression with medication (20 patients) and without medication (30 patients), and untreated depressed subjects were compared over a one-year period using SCL-90-R depression scale scores. **Results:** At baseline, the two treatment groups were comparable in terms of diagnosis and severity of symptoms. Treatment effects were relatively small; patients treated with antidepressants tended to improve, whereas patients treated without drugs deteriorated slightly over one year. Seven years later, treated and untreated subjects no longer differed. **Conclusion:** The results are consistent with previous studies on usual care of depressed patients showing low response rates for non-standardized treatments outside of research settings. Despite a number of methodological shortcomings (small sample size, heterogeneity of subjects and treatments, unusual rating instruments), the results presented here are unique, and provide relevant insight into usual care of depressed patients. This study underlines the importance of standardized psychotherapy and pharmacotherapy in routine practice, of studies investigating the transferability of results of outcome studies across clinical populations, and of quality assurance in primary care psychiatry.

Introduction

Despite nearly four decades of research, there is still much controversy on the best treatment for depressive disorders, and only a few reliable correlates of treatment response have emerged. The 'Practice Guideline for the Treatment of Patients With Major Depressive Disorder (Revision)' of the American Psychiatric Association [1] recommends antidepressant medication for moderate and severe major depressive disorder, and also for mild depressive disorder if preferred by the patient. This tallies with the results from National Institute of Mental Health Treatment of Depression Collaborative Research Program [9] that showed that imipramine plus clinical management produced more improvement and more rapid effects in patients with severe depression than treatment with psychotherapy (cognitive behavior therapy and interpersonal therapy) alone or treatment with placebo plus clinical management. In mild depression, none of the treatments were better than placebo [8]. In contrast, a meta-analysis comparing antidepressant medication to cognitive behavior therapy [7] did not yield any empirical evidence for the superiority of antidepressant treatment over specific psychotherapy in severely depressed outpatients.

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Although randomized clinical trials are the standard method for comparing the efficacy of various treatments of depression, several authors [4,10,12] have questioned the validity of trials on antidepressants. In total, they conclude that the evidence for antidepressant efficacy is lacking because a) placebo treatment results in clinically significant improvement, b) the integrity of placebo-controlled, double-blind, randomized trials is undermined by a penetrable blind that results in biased ratings by drug-favoring clinicians and c) psychotherapy is as effective as antidepressants [14]. In addition, Rush [15] questioned the transferability of results from controlled studies on tertiary-care psychiatric patients to primary-care settings, and urged studies on the transferability of treatments across clinical populations, the naturalistic course of depressive disorders in different treatment settings, and the efficacy of treatments among patients with comorbid conditions.

In a *post hoc* analysis of a naturalistic long-term community study, we analyzed the health status of three groups over one year: 1) depressed subjects receiving medication, 2) depressed subjects treated without medication, and 3) untreated depressed subjects. The aim of our study was to investigate possible differences in effectiveness of naturalistic treatments with and without medication compared to the health status of untreated depressed subjects.

Methods

The Zurich cohort study [3] comprised 4,547 subjects (m = 2,201; f = 2,346) representative of the canton of Zurich, Switzerland, who were first screened in 1978 by means of the Symptom Checklist 90-R [6]. Screened subjects were at ages 19 (males) and 20 (females). In order to enhance the probability of psychiatric syndromes, a subsample of 591 subjects (m = 291; f = 299) was selected to be interviewed in 1979, with two-thirds consisting of high scorers. Follow-up assessments took place in 1980, 1981, 1986, 1988 and 1993. 90.4% of the original subsample (591 subjects) participated in two or more interviews, and 69% remained in the cohort across the observation period of 15 years. Those who dropped out did not differ significantly in their baseline measures in terms of demographic characteristics and psychopathological findings at study entry [3].

The semi-structured psychopathological interview and rating of the social consequences of psychic disturbances for epidemiology (SPIKE) was administered in the subjects' home by psychiatric residents and medical students who had undergone extensive clinical training. This interview schedule assesses a number of somatic and psychological syndromes including depression, anxiety, obsessive-compulsive disorder and others. Two types of depressive syndromes were distinguished, 1) DSM-III-R major depressive episodes and 2) other diagnosis of depression: minor depression (defined by 3 – 4 of nine critical symptoms over at least two weeks requiring depressed mood or anhedonia *plus* social/work impairment) and recurrent brief depression (ICD-10 RBD). In all seven investigations (interviews and mailed questionnaires), symptoms were assessed by the SCL-90-R. For further details of the study design of the Zurich cohort study see [3].

In our analysis, we included subjects who had at least one diagnosis of depression (major depressive episode, minor depression or recurrent brief depression) and were treated 1) by a psychiatrist or a psychologist without drugs or 2) with antidepressant drugs by a psychiatrist or a physician not specialized in psychiatry (general practitioner, internist, etc.). Although all treatments without drugs were conducted by psychiatrists and psychologists, we were unable to determine, on an individual level, whether the intervention was a rather unspecific encounter, general case management, counseling, or specific psychotherapy; it can be assumed, however, that the majority of patients were treated within a general case management framework, and not according to specific guidelines. Half of the subjects treated with medication received tri/tetracyclic antidepressants, the other half benzodiazepines [2]. To improve statistical power, we merged subjects who met our criteria in the first two interview waves (1979 and 1981) into one group. Subjects treated in both periods (4 cases) and subjects with relevant missing data (4 cases) were excluded from the analysis. In the following, we refer to the onset of the treatment period as T1 and to the end of the analyzed treatment period as T2 (treatment period is one year). The follow-up date (8 years after T1) is referred to as T3.

As outcome measure, we chose the SCL-90-R depression score (T-transformed values with x = 50 and s = 10), which we assumed to be relevant and sensitive to change for treatment of depressive disorders. Following the suggestions of *Jacobson* and *Truax* [13], we took the reliable change index (RCI = $1.96 \times \sqrt{2} \times s_x \times \sqrt{(1\text{-rel})} = 11.4$) as the minimum criterion for an individual patient's change to be regarded as statistically significant. As the second criterion for change, we calculated a cut-off value $c = (M_0 \text{ x } s_1 + M_1 \text{ x } s_0)/(s_1 + s_0) = (50 \times 11 + 68 \times 10)/(11 + 10) = 59$; thus, depression scores smaller than c indicated absence of clinically significant depressive symptoms. In cases where both criteria were met, a clinically significant change was assumed. Statistical analysis was done using SPSS for Windows (release 9.0), and comparisons of means by analysis of covariance.

Results

170 subjects had at least one diagnosis of a depressive disorder. Of these, 120 were untreated and 50 were treated. The latter 50 patients were assigned to two treatment groups: thirty subjects were treated by a psychiatrist or a psychologist without any antidepressant medication (group D-); twenty subjects were treated with antidepressant drugs, i.e. tri/tetracyclic antidepressants and benzodiazepines (group D+), 8 by a psychiatrist, 12 by a physician not specialized in psychiatry. In terms of diagnosis and baseline SCL-90-R total score and SCL-90-R depression subscale, there was no significant difference between the two treatment groups (Table **1**). At baseline, the untreated group was different regarding depression scores and diagnosis (only 18.5% of subjects had a major depressive disorder) as compared to the treatment groups. Therefore, we did not conduct statistical comparisons between treated and untreated samples.

At T2, the mean SCL-90-R depression score was 63.37 for subjects treated with drugs and 69.58 for subjects treated without

Table **1** Diagnoses and SCL-90-R scores at T1 in patients treated for depression (n = 50)

	Treatment including medication (D+) n = 20	*Treatment without medication (D-) n = 30*
Female gender	16 (80.0%)	20 (66.6%)
Major depressive disorder	9 (45.0%)	14 (46.7%)
Minor depressive disorder	4 (20.0%)	5 (16.6%)
Recurrent brief depression	11 (55.0%)	14 (46.7%)
	Mean (SD)	***Mean (SD)***
SCL-90-R total score	67.53 (9.34)	68.41 (11.60)
SCL depression score	67.00 (9.69)	67.90 (12.01)
SCL anxiety score	66.67 (12.11)	66.70 (13.46)
SCL somatization score	59.24 (10.29)	56.46 (12.98)

Figures are numbers (%) of patients for gender and diagnoses, mean values for SCL scores.

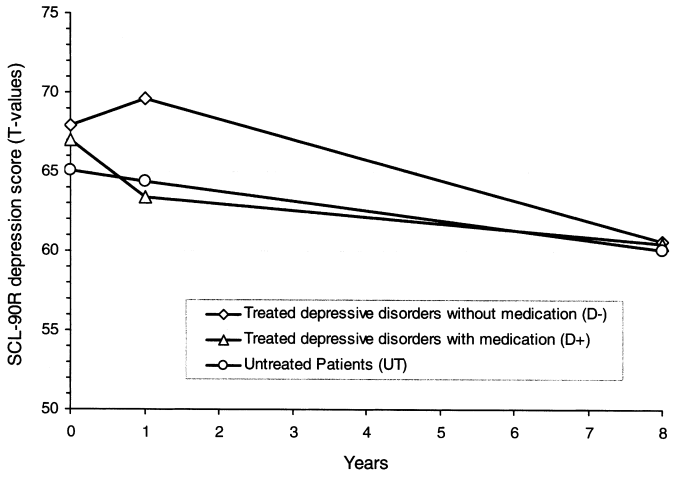

Fig. **1** SCL-90-R depression scores over time in subjects with depressive disorders, depending on different treatment conditions.

drugs. After adjusting for SCL-90-R depression scores at T1, analysis of covariance yielded a significant difference between groups in SCL-90-R depression scores at T2 (p = 0.039). Seven years later (T3), there was no significant difference between groups (Fig. **1**).

In the group of subjects treated with drugs (D+), four patients (20%) improved, 15 (75%) remained unchanged, and one (5%) deteriorated. In the group of subjects treated without drugs (D–), two patients (7%) improved, 22 (73%) remained unchanged, and six (20%) deteriorated. Three patients (15%) in group D+ and two (7%) in group D– showed a clinically significant improvement.

Discussion

To our knowledge, there has been no study comparing depressive disorder treatments with and without drugs in a representative sample of the normal population. In a *post hoc* analysis from a naturalistic long-term community study, we compared the effectiveness of treatments of depressive disorders with and without medication. Although subjects were not randomly assigned to the treatment groups, they were comparable with regard to diagnosis and severity of depressive symptoms at the onset of the treatment period. Thus, the results of our explorative study provide some evidence about the effectiveness of treatment for depression conducted outside of research settings.

The first finding is that treatment without medication was not effective on average. This finding contrasts against the estimates of an overall efficacy of 46 to 60% of specific psychosocial interventions for major depression in primary care [17]. Although all treatments without drugs were conducted by psychiatrists and psychologists, we assume that the majority of patients were treated within a general case management framework, not according to specific guidelines. Therefore, no inferences can be drawn regarding the effectiveness of specific non-drug interventions. A low rate of recovery comparable to our result was found for interventions in primary care patients with major depression treated without a specific protocol [16], whereas non-drug treatments were significantly more effective when applied according to depression-specific guidelines [16].

The second finding was that treatment with medication tended to be effective. This applies to both the average course of depressive symptoms over time and our assessment of clinically significant change. Our response rate of 20% was low compared to the 50 to 60% response rates found in previous studies on drug efficacy for depressive disorders in primary care patients [11,17]. There may be several reasons for this low effectiveness: a) only about half of the subjects treated with medication received antidepressant medication, i.e. tri-/tetracyclic antidepressants, the other half received benzodiazepines [2] that are inferior to tri-/tetracyclic antidepressants with regard to amelioration of core depressive symptoms [5]; b) non-standardized pharmacotherapy of usual care patients turned out to be considerably less effective than standardized pharmacotherapy according to guidelines [16]; c) the attrition rate for patients under tri-/tetracyclic antidepressant medication is high, so therefore treatment duration is frequently inadequate [17].

The third finding is that there were no differences between treatment groups or between treated and untreated subjects at long-term follow-up. This supports the follow-up data from other studies on primary-care treatment of depression [18] as well as controlled trials [8] showing that clinical outcomes are often equivalent for treatment and control groups after a year or longer. Moreover, our finding may be partly explained by the fact that there were no controls for treatment conditions between T2 und T3.

This study has several methodological limitations; the sample size in both treatment conditions was very small affecting the power of statistical analyses. The diagnostic procedure using SPIKE and the depression rating using SCL-90-R are no longer common in outcome studies of depressive disorders where depression-specific diagnostic interview schedules and rating instruments, such as the Hamilton Rating Scale for Depression, are used. This makes a comparison with other studies difficult. Comparing treatments with and without drugs in a naturalistic

study means that the two groups are not randomized, that is, the internal validity is not ensured by controlled conditions. Also, treatment conditions were heterogeneous, and subjects suffered from different types of depressive disorders. Therefore, the results can not be interpreted conclusively in terms of treatment efficacy. Finally, the study design in which T1 and T2 did not refer to onset and end of treatment respectively may account, to a certain degree, for the low effectiveness of the compared treatment conditions, as it is possible that some treatments only began shortly before T2, and were thus not yet conducted for a sufficiently long period to be effective.

Despite a considerable number of methodological shortcomings, the presented data are unique and provide relevant insight into usual care of depressed patients. This study underlines the importance of the implementation of standardized psychotherapy and pharmacotherapy into routine practice, of studies regarding the transferability of results of outcome studies across clinical populations, and of quality assurance in primary care psychiatry.

References

[1] American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder (Revision). Am J Psychiatry, 2000: 157

[2] Angst J. Die depressive Verstimmung als Schaltstelle psychiatrischer Störungen. In: Hell D, ed. Ethologie der Depression Stuttgart: Fischer, 1993: 1 – 15

[3] Angst J, Dobler-Mikola A, Binder J. The Zurich Study – A prospective epidemiological study of depressive, neurotic and psychosomatic syndromes. Eur Arch Psychiatr Neurol Sci 1984; 234: 13 – 20

[4] Antonuccio DO, Danton WG, DeNelsky GY, Greenberg RP, Gordon JS. Raising questions about antidepressants. Psychother Psychosom 1999; 68: 3 – 14

[5] Birkenhager TK, Moleman P, Nolen WA. Benzodiazepines for depression? A review of the literature. Int Clin Psychopharmacol 1995; 10: 181 – 95

[6] Derogatis LR. Administration, Scoring and Procedures Manual-I for the R (revised) version and other instruments of the Psychopathology Rating Scale Series. Baltimore: Johns Hopkins School of Medicine, 1977

[7] DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. Am J Psychiatry 1999; 156: 1007 – 13

[8] Elkin I, Gibbons RD, Shea MT, Sotsky SM, Watkins JT, Pilkonis PA, et al. Initial severity and differential treatment outcome in the National Institute of Mental Health Treatment of Depression Collaborative Research Program. J Consult Clin Psychol 1995; 63: 841 – 7

[9] Elkin I, Shea MT, Watkins JT, Imber SD, Sotsky SM, Collins JF, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry 1989; 46: 971 – 82

[10] Fisher S, Greenberg RP. How sound is the double-blind design for evaluating psychotropic drugs? J Nerv Ment Dis 1993; 181: 345 – 50

[11] Frank E, Rucci P, Katon W, Barrett J, Williams JW, Oxman T, et al. Correlates of remission in primary care patients treated for minor depression. Gen Hosp Psychiatry 2002; 24: 12 – 19

[12] Greenberg RP, Bornstein RF, Greenberg MD, Fisher S. A meta-analysis of antidepressant outcome under "blinder" conditions. J Consult Clin Psychol 1992; 60: 664 – 9; discussion 670 – 7

[13] Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991; 59: 12 – 19

[14] Quitkin FM, Rabkin JG, Gerald J, Davis JM, Klein DF. Validity of clinical trials of antidepressants. Am J Psychiatry 2000; 157: 327 – 37

[15] Rush AJ. Research and clinical practice: bridging the gap. Curr Opin Psychiatry 1994; 7: 3 – 4

[16] Schulberg HC, Block MR, Madonia MJ, Scott CP, Rodriguez E, Imber SD, et al. Treating major depression in primary care practice. Eight-month clinical outcomes. Arch Gen Psychiatry 1996; 53: 913 – 9

[17] Schulberg HC, Katon W, Simon GE, Rush AJ. Treating major depression in primary care practice: an update of the Agency for Health Care Policy and Research Practice Guidelines. Arch Gen Psychiatry 1998; 55: 1121 – 7

[18] Sherbourne CD, Wells KB, Duan N, Miranda J, Unutzer J, Jaycox L, et al. Long-term effectiveness of disseminating quality improvement for depression in primary care. Arch Gen Psychiatry 2001; 58: 696 – 703