Prevention of Major Depression in Complex Medically Ill Patients: Preliminary Results From a Randomized, Controlled Trial

PETER DE JONGE, PH.D., FATIMA BEL HADJ, R.N.
DARIA BOFFA, R.N., CATHERINE ZDROJEWSKI, R.N.
YVES DOROGI, R.N., ALEXANDER SO, M.D.
JUAN RUIZ, M.D., FRIEDRICH STIEFEL, M.D.

Background: *Depression is highly prevalent in patients with physical illness and is associated with a diminished quality of life and poorer medical outcomes.* **Objective:** *The authors evaluated whether a multifaceted intervention conducted by a psychiatric consultation–liaison nurse could reduce the incidence of major depression in rheumatology inpatients and diabetes outpatients with a high level of case complexity.* **Method:** *Of 247 randomized patients, the authors identified 100 patients with a high level of case complexity at baseline and without major depression (65 rheumatology and 35 diabetes patients). Patients were randomized to usual care (N=53) or to a nurse-led intervention (N=47). Main outcomes were the incidence of major depression and severity of depressive symptoms during a 1-year follow-up, based on quarterly assessments with standardized psychiatric interviews.* **Results:** *The incidence of major depression was 63% in usual-care patients and 36% in the intervention group. Effects of intervention on depressive symptoms were observed in outpatients with diabetes but not in rheumatology inpatients.* **Conclusion:** *These preliminary results based on subgroup analysis suggest that a multifaceted nurse-led intervention may prevent the occurrence of major depression in complex medically ill patients and reduce depressive symptoms in diabetes outpatients.*

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Psychiatric comorbidities are highly prevalent in patients with somatic diseases, and are typically associated with poor outcomes in terms of quality of life and also with response to medical treatment.[1–5] Major depression is among the most frequently observed psychiatric comorbidities seen in medical patients, and its presence is specifically associated with poor outcomes. Major depression is highly prevalent in physically ill patients,[6] and it affects quality of life and course of the somatic illness.[7] However, treatment of major depression in somatically ill patients has not been very successful. A series of recent publications has shown that, in general, antidepressant medication results in only modest reduction in depressive symptoms.

Turner et al.[8] reported, in a metaanalysis of FDA-reported trials on antidepressant efficacy, an overall effect size of 0.3, after nonpublished studies were included. Moreover, when only published trials were included, an effect size of

0.4 was found, demonstrating that published trials may have overestimated antidepressant efficacy. Also, Kirsch et al.[9] reported that the efficacy of antidepressant medication is actually satisfactory only for severe depressions (i.e., where the Hamilton Rating Scale for Depression [Ham-D] score is >29), however, by far, most of the depressions in the context of a somatic disease do not fulfill this criterion. Large-scale psychotherapeutic studies on depression in somatic patients, such as the ENRICHD for postmyocardial infarction,[10] have not been successful in reducing depressive symptoms, either. Perhaps a different approach should therefore be followed; namely, to prevent depression in somatic patients at high risk.

Strategies to prevent major depression have been described mainly in the general population,[11] although some have been proposed in physically ill patients,[12] mostly aimed at recurrent depression. Only a few studies have evaluated the primary prevention of depression in physically ill patients.[13,14] As recently argued, such strategies are feasible if an indicator for risk of depression exists.[15] On the basis of our previous work,[16–18] we considered case complexity, a combination of several illness-related and psychosocial vulnerability factors, as an indicator for inclusion in a depression prevention program. We have shown that, with the INTERMED,[19] patients with a somatic disease with a high risk of psychiatric comorbidity can be detected. An intervention trial comparing an active consultation–liaison psychiatric intervention in INTERMED-detected patients was effective in reducing length of hospital stay and increasing quality of life in general-medical patients.[20]

The main objective of the present study was to determine whether a multifaceted intervention by a psychiatric consultation–liaison nurse, focused on coping with disease and enhancing compliance with treatment would prevent the occurrence of depression in medically complex patients. Elsewhere, we have applied this intervention to a sample of 247 high-risk patients recruited at a rheumatology department and a diabetes outpatient clinic, and found that it was successful in reducing the prevalence of major depression, as compared with usual care.[21] Because a substantial proportion of the randomized sample did not suffer from major depression at baseline, we had the opportunity to determine whether the intervention was also capable of preventing incident major depression, and because so few studies have actually looked at this possibility, we performed this subgroup analysis in the present study.

METHOD

Data were drawn from a randomized controlled trial that took place at the University Hospital of Lausanne, Switzerland from 2002 to 2006. The local medical ethics committee had approved the study protocol, which included a written informed consent procedure. Details on the study have been described in a previous report.[21]

Patients

The study is a preplanned subgroup analysis of a randomized, controlled trial. A total of 885 patients were approached for participation: 1) 229 consecutive patients with diabetes mellitus (25.9%) consulting the outpatient clinic of the Division of Endocrinology and Metabolism, and 2) 656 consecutive patients (74.1%) admitted to the inpatient unit of the Rheumatology Service of the University Hospital of Lausanne. Patients were excluded if they did not speak French, suffered from severe cognitive disturbances or terminal illness, were waiting for a planned placement in an institution, were hospitalized for less than 3 days, or showed signs of suicide risk. Eligible patients were included after signing informed consent. For this subgroup analysis, we excluded patients with a current major depressive episode at baseline.

Design

Patients were randomized to "usual care" or a nurse-led intervention arm. Usual care included the possibility that the treating physician could request a regular psychiatric consultation. In the intervention group, a psychiatric liaison nurse had three different intervention options, offered as a single intervention or combined: 1) supportive counseling focused on coping with disease and compliance with treatment, facilitated by a psychiatric liaison nurse; 2) referral to a liaison psychiatrist; and 3) organization of a multidisciplinary case conference attended by the treating physicians, nurses, and a liaison psychiatrist.

Assessments

Case complexity was assessed with the INTERMED, consisting of 20 clinical variables rated by a trained study nurse according to an instruction manual.[16–18] In the INTERMED, information from a medical history-taking is classified into four domains: biological, psychological, social, and healthcare. In each of the four domains, five variables, related to "history," "current state," and "prog-

nosis" are rated 0–3 according to a manual with clinical anchor-points, resulting in a potential score range of 0–60 (higher score indicates increased case complexity). The ratings are not specific, but general, and they apply to any somatic disease. A trained nurse can conduct and reliably rate the INTERMED interview within 15 minutes. A cut-off score of ≥20 was used to indicate a high level of case complexity and, thus, inclusion in the trial.[19] The INTERMED has good interrater reliability (κ: 0.85), test–retest reliability with a period of 1 year between ratings (r=0.75; κ: 0.60), and internal consistency (the estimates of Cronbach α ranging between 0.78 and 0.94 in several samples of patients with somatic illnesses).[22,23]

Outcomes were assessed every 3 months during a 1-year follow-up by a research nurse who was blinded to the intervention status of the patients. Current major depression was assessed with the depression section of the validated French version of the Mini-International Neuro-psychiatric Interview (MINI),[24] a reliable and valid standardized psychiatric interview to assess the presence of psychiatric disorders based on DSM–IV criteria. As the main outcome, we used the cumulative incidence of major depression during follow-up (e.g., present on at least one of the follow-up assessments). Severity of depressive symptoms was assessed with the Center for Epidemiological Studies Depression Rating Scale (CES–D), a 20-item self-report scale to measure depressive symptoms during the last week, with a score range from 0 to 60.[25] The CES–D has been proven to be a valid instrument in physically ill persons.[26] Quality of life was measured at baseline and at 3 months with the validated French version of the SF–36.[27] We used only the two summary scores, the Physical Health Component Score (PCS) and a Mental Health Component Score (MCS),[28] with a scoring range between 0 and 100 (100: optimal functioning). Also, we administered the validated French version of the Visual Analog Scale (0–100; with a higher score indicating higher quality of life) of the EuroQoL.[29]

Statistical Analyses

Patients in both treatment arms were first compared on baseline variables by chi-square tests for categorical data and t-tests for continuous data. Effects of intervention were evaluated by intention-to-treat analyses with respect to 1) incidence of major depression during follow-up (MINI); 2) depressive symptoms (CES–D); and 3) quality of life (EuroQol and SF–36). We evaluated the effects on

incident major depression in two ways. First, we determined the presence of major depression during a 1-year follow-up in patients who completed at least two follow-up assessments. Second, we analyzed the effects on time-related incident major depression by use of a Kaplan-Meier analysis. To analyze the effects on the CES–D assessments, we used a mixed-models approach, since outcomes were assessed repeatedly during follow-up (3, 6, 9, and 12 months post-randomization).[30] We tested a mixed model consisting of treatment allocation as a factor, and baseline CES–D and timing of the assessment as covariates. A preplanned subgroup analysis was conducted comparing the effects for rheumatology and diabetes patients separately. For the effects on quality of life at 3 months, we used linear regression, controlling for corresponding baseline functioning.

RESULTS

Of the 885 patients who were assessed for eligibility, 184 were excluded because of the exclusion criteria, and 454 patients did not have a high enough level of case-complexity. Of the remaining 247 patients, 139 were excluded from the present analyses because they had a major depression at baseline or missing data on baseline depression rating (N=8), resulting in a study sample N of 100 (see Figure 1). Of these patients, 35 had diabetes (Type 1: N=8; Type 2: N=22; other: N=5), and 65 were recruited from the rheumatology ward (inflammatory-based disorder: N=15; degenerative or pain: N=41; age-related: N=1; other [mainly fibromyalgia]): N=8).

Patients in the Usual-Care and Intervention arm did not significantly differ with regard to sociodemographic variables and baseline measurements except for a nonsignificant difference in education level and severity of depressive symptoms (Table 1). In subsequent analyses (mixed-models analyses), we therefore controlled for baseline severity of depression symptoms. In the Intervention arm, most patients (N=41/47; 87.2%) received at least one intervention conducted by the psychiatric liaison nurse (median: 8 sessions; interquartile range [IQR]: 3.5–11). The interventions, performed as single interventions or combined, consisted of "facilitating emotional expression" (70.7%), "giving practical advice" (65.9%), "promoting life-narrative" (43.9%), and "psycho-education" (48.8%). A minority of patients received psychiatric consultations (N=7; 17.0%), psychiatric advice to the treating physician (N=2; 4.8%), interdisciplinary case-conferences (N=3; 7.3%), or no additional intervention (because

there was no indication for treatment or the patient lacked motivation; N=6; 12.8%).

The Intervention condition was associated with a lower incidence of major depression (36.4% versus 63.2%; p=0.02; Table 2). In logistic-regression analysis, the intervention was associated with a decreased risk of major depression (odds ratio [OR]: 0.33; 95% confidence interval [CI]: 0.13–0.88; p=0.02), which largely remained although the statistical significance disappeared (OR: 0.39; 95% CI: 0.14–1.09; p=0.14). When comparing the treatment arms on time-related incidence of major depression by use of a Kaplan-Meier survival analysis, we found a (tendency to) a prolonged event-free survival in the Intervention arm (log-rank: 3.1; p=0.08; estimated mean time to event, Care-As-Usual: 7.9 months (95% CI: 6.7–9.0) and Intervention: 9.2 (95% CI: 8.0–10.4). Using Cox regression analysis, we found a nonsignificant decreased risk of major depression (OR: 0.60; 95% CI: 0.31–1.16; p=0.13), which was somewhat reduced after controlling for baseline CES–D (OR: 0.69; 95% CI: 0.35–1.36; p=0.29).

Mixed-models analysis of the differences on CES–D yielded a 1.6-point decreased level of depressive symptoms in the Intervention arm, after controlling for baseline CES–D and timing of assessment (95% CI: –1.2 to 4.4; p=0.26). Effect sizes for diabetes and rheumatology patients separately were 6.2 (95% CI: 1.7–10.6; p=0.007) and 1.3 points (–2.2 to 4.9; p=0.46), respectively (Figure 2). Controlling for baseline functioning, Intervention was associated with OR: 2.9 (95% CI: –1.2 to 6.9; β=0.14; p=0.16), higher scores on the PCS: (OR: 2.1; 95% CI: –3.9 to 8.1; β=0.09; p=0.48), higher scores on the MCS: OR: 8.3; 95% CI: 0.1–16.5; β=0.22; p=0.047), and a higher score on the EuroQol VAS.

Rheumatology patients reported significantly more pain, assessed with the EuroQol–5 at baseline (no pain: 0.0%; moderate pain: 53.8%; severe pain: 46.2%) than di-

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FIGURE 1. Patient Flow Chart
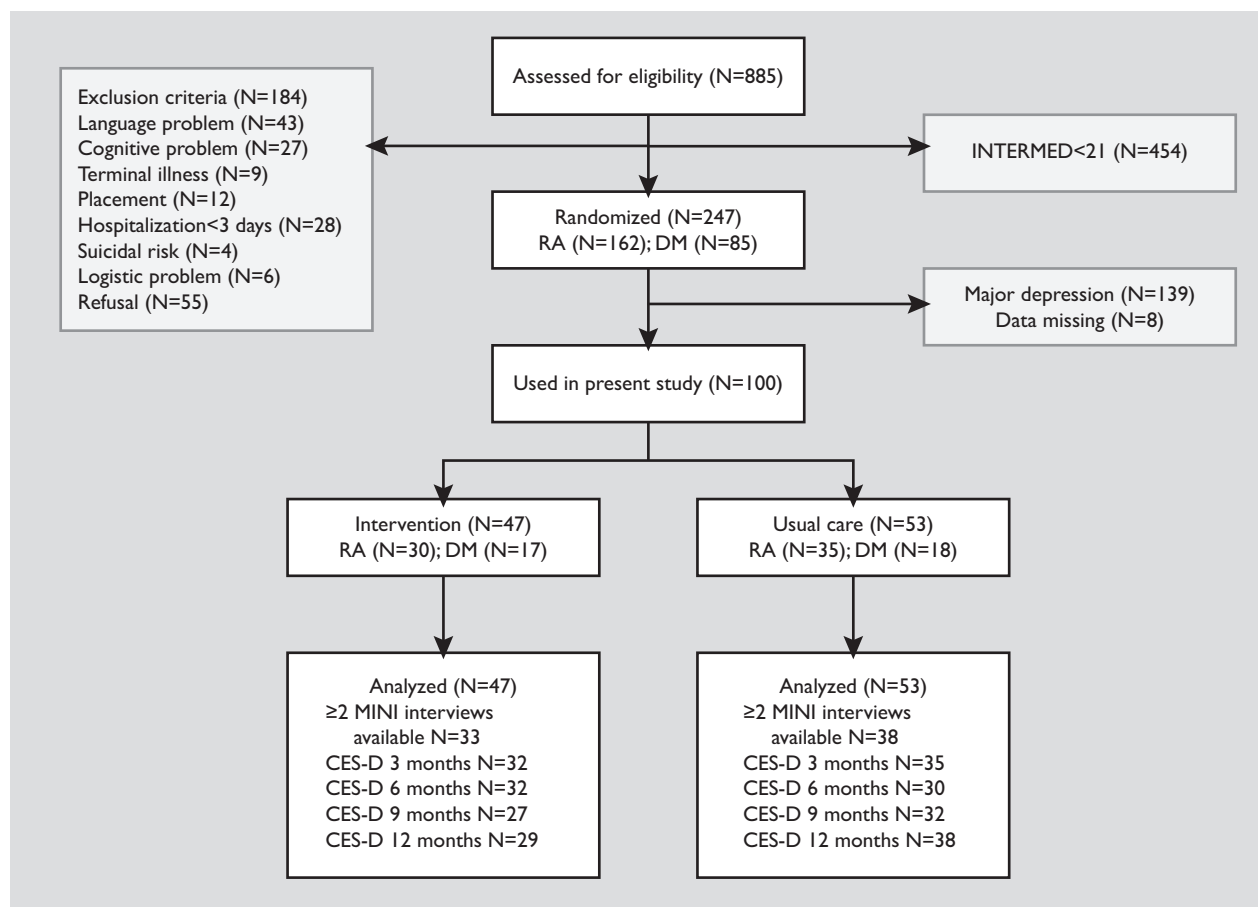
RA: rheumatoid arthritis; DM: diabetes mellitus.

abetes patients (no pain: 27.1%; moderate pain: 65.7%; severe pain: 17.1%; $\chi^2=17.0$; p<0.001), and more depressive symptoms (mean CES–D noted in rheumatology patients: 21.3 (standard deviation [SD]: 8.7); diabetes patients: 17.4 (SD: 10.1). The intervention was effective in preventing major depression in subjects with no or moderate pain (intervention: 30.4%; Care-As-Usual: 60.0%; $\chi^2=4.2$; p=0.04) but not in patients with severe pain (Intervention: 50.0% versus 69.2%; $\chi^2=0.9$; p=0.35). The intervention was effective in preventing major depression in patients with a baseline CES–D>20 (Intervention: 50.0% versus 85.7%; $\chi^2=5.3$; p=0.02) but not in patients with a baseline CES–D ≤20 (Intervention: 26.3% versus 35.3%; $\chi^2=0.3$; p=0.56).

DISCUSSION

The aim of this study was to evaluate whether a preventive intervention by a psychiatric nurse targeted at complex medically ill patients could reduce the incidence of major depression and depressive symptoms. Results showed that patients in the intervention arm of the study suffered less frequently from incident major depression during the 1-year follow-up. Moreover, reductions in depressive symptoms were observed in diabetes outpatients, and, on one of the three quality-of-life indicators, a positive effect of intervention was found.

With respect to depressive symptoms, we found that intervention effects were restricted to outpatients with diabetes. We explored two options to explain this finding. First, the differential effectiveness may have been due to the possibility that rheumatology patients had more depressive symptoms at baseline and that our intervention, dominated by supportive counseling by a psychiatric nurse, was effective only for patients with relatively mild depressive symptoms. This explanation was not supported

TABLE 1. Comparison of the Two Treatment Arms on Baseline Variables

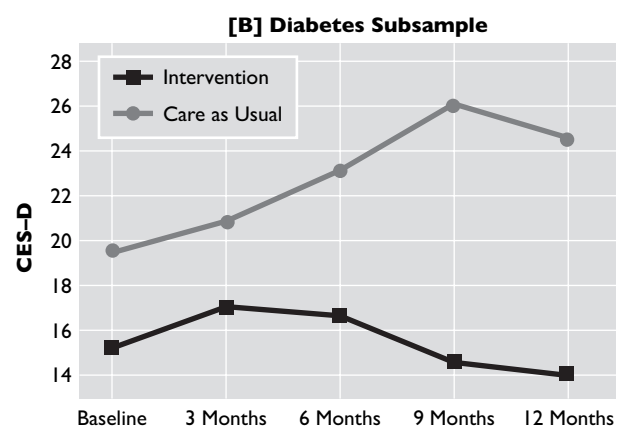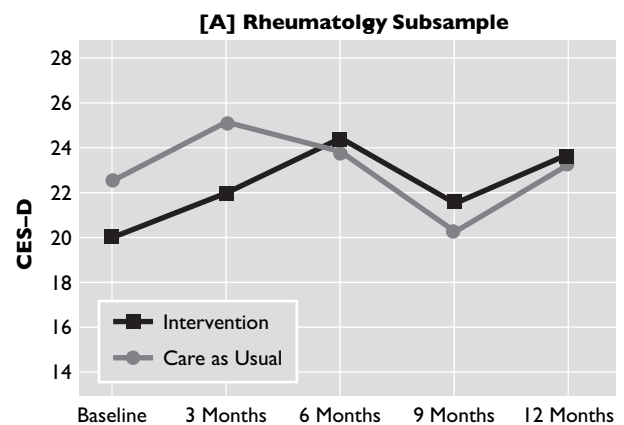|	Intervention (N=47)	Usual Care (N=53)	p
Mean age, years (SD)	52.4 (13.9)	53.4 (16.7)	0.76
Female sex	61.7%	54.7%	0.48
Level of education			0.09
Low	34.0%	55.8%	
Middle	34.0%	25.0%	
High	31.9%	19.2%	
Professional level			0.16
Low	31.9%	45.3%	
Middle	53.2%	35.8%	
High	14.9%	18.9%	
Rheumatology inpatients	36.2%	34.0%	0.49
Diabetes outpatients	63.8%	66.0%	
Depressive symptoms (CES–D; mean, SD)	18.3 (8.8)	21.5 (9.7)	0.09

SD: standard deviation.

TABLE 2. Comparison of Intervention Arm and Usual-Care Arm on Outcomes at 3, 6, 9, and 12 Months Post-Randomization

	Intervention	Usual Care	p
Major depression	36.4%	63.2%	0.02
Depressive symptoms, mean (SD)			
3 months	20.0 (11.8)	23.8 (11.3)	0.18
6 months	21.5 (12.8)	23.6 (12.8)	0.53
9 months	18.4 (10.5)	22.6 (13.9)	0.20
12 months	19.4 (12.1)	23.8 (14.9)	0.20

SD: standard deviation.

FIGURE 2. Course of Depressive Symptoms (CES–D) for Intervention Versus Usual-Care Patients in the Rheumatology and Diabetes Subsamples

by our data, given that most effects were observed in patients with higher levels of depressive symptoms at baseline. A second explanation seems more plausible; namely, that rheumatology inpatients had more pain complaints, which, in our present study, may have reduced the effects of the intervention. In support of this hypothesis, we found that rheumatology patients had more pain complaints and that our intervention was specifically effective in patients without severe pain complaints at baseline.

The multifaceted psychiatric interventions have been mainly facilitated and organized by psychiatric liaison nurses. Only patients who needed further assessment or psychopharmacological treatment were referred to a liaison psychiatrist, or advice concerning psychiatric management was given to the treating physician, which happened in only a minority of patients. Interdisciplinary case conferences were only rarely organized. This approach to preventing depression in complex medically ill patients therefore seems feasible and effective, specifically in diabetes patients and/or patients without severe initial pain complaints.

The level of depressive symptoms at baseline in our sample of patients was around 20 on the CES–D scale. This means that most patients might be considered to have subclinical depression at the start of the study. Our intervention prevented the onset of depression in this vulnerable group by means of relatively simple interventions conducted by a nurse. Recently, a metaanalysis was done on the effects of psychological treatments of subthreshold depression,[31] which reported an OR of 0.70 (95% CI: 0.47–1.03) for preventing the onset of major depression. Of these studies, only one[32] was conducted in medically ill patients, and the intervention, interpersonal counseling, was effective in reducing depressive symptoms. Most of the other interventions described in this metaanalysis were rather structured, cognitive–behavior therapy-based interventions. In contrast, our intervention was less structured, multifaceted, and, in general, more focused on coping,

well integrated into clinical care, and apparently more effective (OR: 0.33; 95% CI: 0.13–0.88). Perhaps this indicates that depression prevention strategies for subthreshold depression are effective specifically when they are flexible. Another possibility is that our findings stress the importance of indication criteria for intervention, which was supported by the substantial differences in effectiveness among our two patient subsamples.

Some limitations need to be considered in interpreting our findings. Because our findings were based on a subgroup analysis of a randomized, controlled trial, they need to be considered as preliminary, and replication is warranted. Moreover, we did not document the exact care given in the usual-care group and did not have information on antidepressant use at baseline. However, it is well known that only a minority of physically ill patients with psychiatric problems actually receive psychiatric care, which may even be worse with respect to patients suffering from subclinical problems, as in our subsample. Another limitation is that, at baseline, significant differences have emerged on the CES–D scale between the two treatment conditions. However, in order to prevent bias due to this difference, in multivariate analyses, we subsequently controlled for baseline CES–D, which did not substantially alter our findings.

In conclusion, we found that in high-risk patients with somatic disease and a high level of case complexity, a nurse intervention was effective in reducing the incidence of major depression. Future efforts should further explore targeting relevant patient groups for which these interventions work, and confirmation in larger samples needs to be sought.

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