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Authors: de Roten Y, Ambresin G, Herrera F, Fassassi S, Fournier N, Preisig M, Despland JN

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Yves de Roten, & Gilles Ambresin, Fabrice Herrera, Sylfa Fassassi, Nicolas Fournier, Martin Preisig, Jean-Nicolas Despland

Author Note

Yves de Roten, Fabrice Herrera, and Jean-Nicolas Despland, Institute of Psychotherapy, Department of Psychiatry, University Hospital Centre and University of Lausanne, Switzerland; Sylfa Fassassi, Service of General Psychiatry, Department of Psychiatry, University Hospital Centre and University of Lausanne, Switzerland; Martin Preisig, Centre for Epidemiology and Psychopathology, Department of Psychiatry, University Hospital Centre and University of Lausanne, Switzerland; Nicolas Fournier, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland; Gilles Ambresin, Institute of Psychotherapy, Department of Psychiatry, University Hospital Centre and University of Lausanne, Switzerland; Honorary Research Fellow, General Practice and Primary Health Care Academic Centre, The University of Melbourne, Melbourne, Australia.

The two first authors contributed equally to the writing of this paper.

Correspondence concerning this article should be addressed to Gilles Ambresin, Institut Universitaire de Psychothérapie, Bâtiment Les Cèdres, Site de Cery, CH-1008 Prilly, Switzerland. Ph: +41.21.314.18.92. Fax: +41.21.314.27.84. E-mail: gilles.ambresin@chuv.ch.

Efficacy of an Adjunctive Brief Psychodynamic Psychotherapy to Usual Inpatient Treatment of Depression: Results of a Randomized Controlled Trial

Introduction

Depression is among the most common reasons for psychiatric hospitalisation (Schneider et al., 2005; Stensland et al., 2012). Inpatients with depression have a high degree of severity, comorbidity, chronicity and treatment resistance. They belong to the most severe and disabled patient populations (APA, 2010). Meta-analyses have consistently shown the advantage of combined treatment for patients with depressive disorders that are complicated by comorbidity, chronicity, treatment resistance, recurrence, or high severity (Cuijpers et al., 2009; de Maat et al., 2007; Imel et al., 2008). Current clinical guidelines recommend a combination of pharmacotherapy and psychotherapy to treat either moderate to severe depression (APA, 2010; NICE, 2009) or severe depression only (DGPPN, 2012). Different psychotherapeutic interventions for depression such as cognitive-behavioral (CBT), interpersonal (IPT), and psychodynamic therapies have shown efficacy with no significant association between effect size and type of psychotherapy (Barth et al., 2013). Furthermore, by both mental health professionals and their patients value psychotherapy alone or the combination of psychotherapy and pharmacotherapy is highly as a way of hastening recovery, either through additive effects or by compensating for the limitations of monotherapy (Lelliott and Quirk, 2004; Pampallona et al., 2004; Peeters et al., 2013).

Some studies have documented the possible advantages of brief psychodynamic psychotherapy combined with antidepressants, as compared to antidepressants alone. One study found that although both groups experienced significant improvement, the combined treatment group had fewer treatment failures, better work adjustment, better global functioning, and a lower rate of hospitalization than the medication alone group (Burnand et al., 2002). De Jonghe et al. (2001) showed that patients found combined treatment significantly more acceptable than medication alone. The patients receiving combined treatment were significantly less likely to drop out and were also more likely to recover. The authors concluded that combined therapy is preferable to pharmacotherapy alone in treating ambulatory patients with major depression (De Jonghe et al., 2001). A more recent study found no difference in remission rates at the end of a 6-month acute treatment phase between a group of patients who received a brief psychodynamic psychotherapy combined with an SSRI and a group of patients who received medication alone (Maina et al., 2009). However,

more patients in the combined group achieved sustained remission at the end of the follow-up period compared with patients who had only received medication during the acute phase.

Several recent position papers call for better quality of inpatient care (Craig, 2016; Porter et al., 2016). These position papers suggest that the positive aspects of inpatient admission, including the opportunity for assessment and intensive treatment, should be emphasized (Porter et al., 2016). The treatment options for better quality care include psychotherapy. Psychological treatment may improve the recovery of depressed inpatients and reduce their suffering for themselves as well as that of their relatives (Porter et al., 2016). In a systematic review and meta-analysis based on 12 studies, Cuijpers et al. (2011) showed a small (ES = 0.29) but robust additional effect of psychological treatment on depression in depressed inpatients (Cuijpers et al., 2011). A previous meta-analysis (Stuart and Bowers, 1995), based on 4 controlled studies, showed higher effect sizes with a difference between self-report measures (ES = 1.13) and independent observer measures (ES = 0.38) at discharge from the hospital in favor of adding CBT to the usual treatment. These results contrast with a review of 6 studies on inpatients with depressive disorder (Huber, 2005) that showed less conclusive results. Three studies showed an additional effect of psychotherapy (corresponding to a moderate ES). Combined treatment was superior to pharmacotherapy in terms of remissions rates and relapse rates. Additionaly, three studies showed no additional effect. The results were clearer for more severely depressed inpatients or chronic inpatients. The author concluded that combined treatment is advantageous in the case of treatment resistance, or chronic or severe illness, and depends on patient preferences. Although these reviews found some indications for the positive effects of combined treatment for depressed inpatients, the results are still ambiguous. The number of studies included in the reviews was relatively small and their quality was not optimal. The vast majority of the included studies had relatively small sample sizes. Good-quality studies with larger sample sizes are needed to further examine the effects of psychotherapy for depressed inpatients (Cuijpers et al., 2011).

Most of the above mentioned studies reported on the effectiveness of cognitive and/or behavioral inpatient psychotherapies. Cuijpers et al. (2011) retrieved only 3 studies out of 12 did not involve CBT, among which a single study involved interpersonal psychotherapy. Huber (2005) reported on 5 CBT studies and on one client-centered psychotherapy study, while Stuart and Bower (1995) only examined cognitive therapy. Early research on the effectiveness of outpatient psychotherapies for depression also found evidence for the effectiveness of CBT first. The place of psychoanalytic treatment within psychiatry had been controversial for a moment (Gabbard et al., 2002); however, an increasing scientific litterature

has since shown the effectiveness of psychotherapy in treating depression (Fonagy, 2015). Recent meta-analyses converge to conclude that the differences between psychotherapies in treating depression are small and unstable (Barth et al., 2013). Some people may respond better to interventions other than CBT (Barth et al., 2013). It may also be true for inpatients; hence, the potential of psychodynamic psychotherapies to be useful for inpatients warrants further research.

The purpose of the current study was to estimate the relative efficacy of adjunctive psychodynamic psychotherapy compared to the usual psychiatric and pharmacologic treatment on the short- and long-term outcomes of inpatients with either moderate or severe depression.

Methods

Procedure and study design

This single-blind one-month randomized controlled add-on trial compared (1) an intervention arm with (2) a treatment-as-usual arm (TAU). Inpatients in the intervention arm received an intensive brief psychodynamic psychotherapy (IBPP) as an add-on therapy to the TAU. IBPP was initiated within a few days after admission. When patients were discharged before the end of IBPP, IBPP continued on an outpatient basis. This RCT was single-blind as the participants were aware of their allocation when they received additional psychotherapy. Rationale, design and procedure of the study was extensively presented elsewhere (Ambresin et al., 2012). The University Ethical Committee approved the research protocol (April 12, 2010).

Participants

For inclusion, patients hospitalized in the university psychiatric hospital had to: (1) meet DSM–IV criteria for unipolar major depressive episode (MDE); (2) be 18-65 years of age, (3) have a Montgomery-Asberg Depression Rating Scale (MADRS) > 18, and (4) have sufficient command of French. Exclusion criteria were limited to bipolar disorders, psychotic disorder, persistent substance use/abuse which might affect brain function (memory, level of consciousness, cognitive abilities) thereby impairing the individual from participating and benefiting from psychotherapy. The following comorbidities were considered as relative contraindications: Axis II paranoid, schizoid or schizotypal, borderline personality disorder, antisocial personality disorder, recent suicide attempts necessitating residential or day treatment and acute risk for suicide, and cognitive impairment.

Outcome measures

The outcome measures of depression severity were: (1) the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), a clinician rating measure in 10 items, and (2) the Quick Inventory of Depressive Symptom - self-rated version (QIDS-SR_{16}) (Corruble et al., 1999), a 16-item self-report measure of depressive symptoms, which provides a sensitive measure of patient change in inpatient setting. Construct validity of MADRS has been demonstrated in an inpatient sample (Davidson et al., 2005) The Global Assessment of Functioning (GAF) was included as a measure of functioning. For the MADRS, treatment response was defined a priori as a reduction in symptom severity of 46% or higher of the baseline score and remission as a score of 7 or less, based on cut-off scores determined in a large inpatient population (Riedel et al., 2010); for the QIDS-SR_{16} response corresponded to a symptom reduction >= 50%, and remission as a score of score of 5 or less (Rush et al., 2006).

The diagnostic assessment relied on the French version of the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), which elicits DSM-IV depression symptoms and revealed excellent inter-rater (kappa=0.93) and fair test-retest (kappa=0.62) reliability for MDE (Preisig et al., 1999). These semi-structured interviews were conducted by trained and experienced clinical psychologists who were independent and blind for treatment allocation. The efficacy of treatment was evaluated 4 weeks after the beginning of the treatment and 3 and 12 months post-hospitalization in terms of a naturalistic follow-up. Pre-treatment, post-treatment and all follow-up assessments were conducted face-to-face. Kind of treatment patients received after discharge were also assessed 3- and 12-month follow-up encounters. Research psychologists (master level), who were not involved in the inpatient care and not located in the hospital, administered all questionnaires except for the DIGS. Research psychologist were blind to treatment allocation and were completely independent from the clinical team. Inter-rater reliability for the MADRS was obtained from 15 audiotaped interviews (mean *ICC*(2,1) = .88, range = .68 - .96).

Treatment conditions

Psychosocial Treatment-As-Usual (TAU). TAU followed the Practice guideline for the treatment of patients with Major Depression (APA, 2010), which represents the best level of practice for a minimal pharmacological and psychosocial treatment condition usually applied to hospitalized patients. A first interview of 45 minutes defined a treatment plan made up of patient, nurses, medical, and social objectives. Clinical management was defined as supportive interventions of 20 to 25 minutes, addressing psychopharmacological issues when

necessary, delivered twice a week by a psychiatric resident. Weekly, nurses delivered two 30-minute encounters aiming at developing the patient's psycho-educational skills, empowerment, and individualized treatment. Social workers, ergo-, physio-, and art-therapist interventions were integrated into the treatment as required by the patient's needs. Therapeutic staff met once a week to adapt the treatment plan. All participants were requested to participate in six group sessions of psychoeducation. Pharmacotherapy as prescribed by the referring psychiatrist followed the rules of the World Federation of Societies of Biological Psychiatry (Bauer et al., 2002).

Inpatient Brief Psychodynamic Psychotherapy (IBPP). The intervention model was based (1) on the manual of psychodynamic treatment of depression developed by Bush, Rudden, & Shapiro to help the therapy focalize on relevant depression foci (Busch et al., 2004), and (2) on the manual on brief psychodynamic psychotherapy developed by Despland, Michel, & de Roten (Despland et al., 2010) for the work on transference, personality organization and conflictual themes. The IBPP was a very brief intervention programme including 12 sessions over 4 weeks (Ambresin et al., 2009). It has been implemented as an add-on therapy to inpatient TAU. IBPP patients received an amount of inpatient treatment in addition to IBPP which was similar to TAU patients. The initial hypothesis (see Clinical Vignette) was based on the dynamic relationship established between the therapist and the patient during the first three sessions (pre-transference), on the patient's present crisis, and on the dynamics that formed the core of his/her depressive episode. Following sessions focalised on helping the patient to gain a fuller understanding of the psychological factors that had led to the emergence of depressive symptoms and to address his/her vulnerability to those dynamics. IBPP made use of the transference and the transference relationship was interpreted whenever it was possible and relevant. Final sessions addressed the patient's feelings and fantasies about termination as well as the decision regarding a longer-term therapy or ongoing psychiatric treatment if necessary. This brief intervention aimed at achieving a constructive change in the patient and at bringing the patient's psychiatric problems into remission.

Treatment integrity

Prior to the study, the therapists attended training in a weekly seminar dedicated to IBPP for 6 months before they started their first IBPP with a patient. They were monitored for adherence and competence by receiving weekly individual supervision and continued participation to the training seminar. All therapists (18 psychiatrists and 5 psychologists) had completed (or were in advanced stage of completing) 5 years of psychotherapy training. The Psychotherapy

Process Q-set (PQS) (Jones, 2000) was used to check therapist's adherence to IBPP. The PQS is an instrument designed to describe psychotherapy process at the level of an individual psychotherapy session. It consists of 100 items describing therapist behaviours, patient behaviours, and therapist-patient interactions. The characteristic elements of a therapeutic session can then be compared to ideal treatment prototypes for specific psychotherapies developed by experts (e.g., CBT, IPT, STDP). A panel of 7 experts developed a prototype of IBPP using the PQS. The prototype was then used to assess the extent to which the treatment conformed to the other prototypes. Two independent raters coded two sessions (the second and the penultimate) in a sample of 39 IBPP cases with the PQS. Inter-rater reliability assessed 18 sessions (23%) was fairly good with an intra-class correlation coefficient *ICC*(2,1) of .661 (range = .433 to .767). Comparison was also done with prototypes of the two main empirically-validated psychotherapeutic approaches for depression (CBT and IPT) and a prototype of non-specific short-term dynamic psychotherapy (STDP).

Statistical analysis

All data were analyzed using an intent-to-treat analysis (ITT, n= 149), and a per-protocol with sufficient amount of treatment (at least 6 sessions of therapy) analysis (PP, n= 131, Supplementary tables 1 to 3). All statistical analyses were carried out using Stata v. 14 (StataCorp, College Station, TX, USA). Continuous data distribution was assessed using Normal QQ-plot. Distribution of Gaussian data was summarized as mean and standard deviation. Distribution of non-Gaussian data was summarized as median and interquartile range. Differences between two groups in continuous data distribution were assessed using the Student's t-test in case of Gaussian data, or using the Wilcoxon-Mann-Whitney rank sum test in case of non-Gaussian data. Categorical data were presented as frequency and group percentage. Distribution differences in categorical data were assessed using the Chi-Squared test, or the Fisher's exact test in case of insufficient sample size.

Mean effect sizes were reported using Cohen's d and 95% confidence intervals in case of two independent groups (treatment effects), and using Pearson's r correlation coefficient and 95% confidence intervals in case of two paired groups (time effects). We used logistic regression to assess association between covariates and the probability of treatment response or remission at different time points. Analyses were adjusted for sex, age, recurrence, chronicity and severity of depression at baseline as adjustment for known prognostic variables can lead to substantial increases in power in the analysis of randomized control trials (Kahan et al., 2014). Results of logistic regression models were presented at Odds ratios, 95%

confidence intervals and p-values. We used linear mixed models to assess associations between covariates and continuous outcomes measured repeatedly over time. A first-order autoregressive covariance structure was used. Results of linear mixed models were presented as raw coefficient, 95% confidence intervals and p-values (Supplementary table 4).

All statistical tests were conducted using a two-tailed type-I error level of 5%.

Missing data handling

We carried out Multiple Imputation using Chained Equations (MICE) to handle missing data (Supplementary tables 5 and 6) in analysis of outcomes (MADRS, QIDS, and GAF scores trajectories). Missing data on outcome scores at post treatment, 3 months and 12 months (MADRS, QIDS, and GAF) and covariates (Chronicity and Recurrence) were imputed. Truncated linear regression modelling was used for the outcomes variables, while logistic regression modelling was used for the two covariates. We report within group (time) and between group (treatment) effect sizes for outcome analysis based on imputed dataset.

Differences in characteristics' distribution between individuals with complete and incomplete data were assessed using Student's t-test (for Gaussian distribution), Wilcoxon-Mann-Whitney rank sum test (for non-Gaussian distribution), or Chi-squared test (for categorical data). No association was found between missing status and patients' characteristics, except for Age and MADRS score at 12 months, where an older age was associated with a higher proportion of response.

MICE was carried out using Stata v.14. Number of imputations was set to 50. Treatment, Gender and Age were used as auxiliary variables, with no interaction terms. As a diagnostic (sensitivity) check of our imputation model, we compared the distribution of observed and imputed values, for each variable, and no differences were found.

Results

Patient flow

The numbers and percentages of retained participants at post-treatment as well as at the 3-month and 12 month follow-up points are shown in the CONSORT flow chart (Figure 1). One hundred and fifty-three participants were randomized. Of these, 76 participants were allocated to receive IBPP and 73 to receive treatment-as-usual.

The proportion of complete cases (patients with all 4 scores measurements available) ranged from 57.0% to 71.0%, depending on the score and the treatment in consideration (Supplementary Table 5). For the outcome variables, the percentage of missing data ranged from 20.8% to 30.2% in the ITT analysis (Supplementary Table 6).

Baseline demographics and clinical characteristics

A majority of the patients were characterized by features of complicated depressive disorder (Table 1). Within the ITT sample, depression severity was severe when measured with the MADRS and the QIDS. Nearly half of the sample received a diagnosis of recurrent major depressive disorder as determined by the DIGS. Depression was qualified as chronic (defined as 2-year duration) for a similar proportion of the participants. The participants were about 30 years of age at depression onset; among the participants about a fourth reported a first episode before the age of 20. Fifty-eight percent of the sample reported a history of suicide attempts. More than 9 patients out of 10 presented with an axis I comorbidity, and more than a third presented with a comorbid axis II diagnosis. Their functioning was moderately to seriously impaired. The participants were frequently divorced or widowed and had completed secondary education (11 years of education). A majority of the participants were unemployed. On average, the participants were discharged after 5 weeks of inpatient stay. None of the baseline characteristics differed significantly between the 2 groups.

Pharmacological treatment

Three patients out of 4 had an antidepressant medication at baseline (Supplementary Table 7), mostly SSRIs (56.1%) or SNRIs (32.7%). Just more than a third of the patients received an antipsychotic medication. Use of mood stabilizers was not very common (9.8%) while 3 patients out of 5 received benzodiazepines. Nearly a fourth of the patients received a second antidepressant and a third of the patients received a second benzodiazepine. None of the baseline pharmacological treatment characteristics differed significantly between IBPP and TAU groups.

Treatment integrity

Each patient in the ITT sample received a mean of 8.5 (*SD* = 4.2) IBPP sessions (median 10.5, IQR = 6-12). The patients in the per-protocol sample received a mean of 10.8 (*SD* = 1.8) IBPP sessions (median 12, IQR 10-12).

The prototype of ideal IBPP was correlated with PQS ratings of the second and the penultimate psychotherapy sessions (see Ablon & Jones, 2002 for a description of the method). The mean correlation with IBPP prototype was r = .43 (*SD* = 0.09), which provides an index of how closely the treatment adhered to the process prescribed by the experts in the IBPP prototype. The mean correlations with the IPT prototype (r = .28) and CBT prototype (r = .36) were lower. The correlations were similar to those found between IPT and the IPT prototype in the TDCRP study (Ablon & Jones, 2002), between psychodynamic psychotherapy and the psychodynamic prototype (Ablon & Jones, 1998), and between long

term psychodynamic psychotherapy and the psychodynamic prototype (Katzenstei, 2007). Adherence to IBPP was greater than adherence to STDP (session 2: t_{38} = 24.38, p = .000; penultimate session: t_{38} = 24.72, p = .000), IPT (session 2: t_{38} = 7.27, p = .000; penultimate session: t_{38} = 4.73, p = .000) and CBT (session 2: t_{38} = 2.03, p = .049; penultimate session: t_{38} = 2.80, p = .008). Therfore, the treatment integrity for IBPP was therefore acceptable.

Treatment effects on depression severity and functioning

The ITT sample showed significant improvements among both groups in depression severity at every time of measure (between the baseline and all follow-up points). The effect sizes for the improvement in the 2 groups were in the medium range.

Small to medium effect sizes of treatment were observed at every follow-up point when measured with the MADRS (Table 2). Specifically, a medium treatment effect of d = 0.46 was observed at the 3-month follow-up and small effects of d = 0.39 and d = 0.32 were observed at post-treatment and at the 12-month follow-up, respectively. When measured with the QIDS, medium size effects of treatment were significant at the 3-month follow-up.

The effect size of time for general functioning indicated a decrease of GAF at the post-treatment follow-up point, but effect sizes were no longer significant at the 3-month follow-up and 12-month follow-up points. Similarly to the depression severity measures, GAF showed significant positive treatment effects at the 3-month follow-up point. The effect of treatment on global functioning (d = -0.52) was higher than those for the depression measures.

The Fisher test provided strong evidence for the global effect of treatment and the interaction between treatment and time for the MADRS (F(4,7005.2) = 3.89, p = 0.004) and the QIDS (F(4,7450.6) = 3.36, p = 0.009) after adjusting for sex, age, recurrence, chronicity and severity at baseline. Slight evidence for the effect of treatment and an interaction between treatment and time was found with the GAF (F(3,4451.5) = 2.23, p = 0.083). Linear mixed model analyses revealed a significant time by treatment group interaction for the MADRS (Figure 2), the QIDS, and the GAF at the 4-month follow-up (MADRS F(1,2785.7) = 5.40, p = 0.020; QIDS F(1,1713.9) = 6.77, p = 0.009; GAF F(1,7283.1) = 6.70, p = 0.010) after adjusting for sex, age, recurrence, chronicity and severity at baseline. Age and sex had no effect on the outcome variables (MADRS and QIDS) for all of the models using LGMM analysis. Recurrence and chronicity had negative significant effects on the outcomes.

The effect sizes were similar for both measures of depression severity when using the non-imputed dataset (results available on request). Estimations of the magnitude of the effect sizes remained relatively unchanged after using multiple imputation. Multiple imputation narrowed a vast majority of the 95%CI.

Treatment response and remission

The percentage of participants showing a response was significantly higher in the IBPP group than in the TAU group at all of the measurement points when measured with the MADRS (Table 3). By 12 months, 31.7% of the IBPP group but only 14.3% of the TAU group were in remission. The participants allocated to the IBPP group were more likely to display a response at all of the measurement points and were also more likely to be in remission at 3 and 12 months than participants allocated to the TAU group after adjusting for sex, age, recurrence, chronicity, and the severity of depression at baseline. The estimates of the ORs of the response and remission indicated a significant advantage of adjunctive IBPP to TAU alone at the 3-month follow-up when measured with the QIDS after adjusting for sex, age, recurrence, chronicity, and the severity of depression at baseline.

The odds ratios of response and remission were higher and the 95%CIs were wider when estimated using the non-imputed cases (results available on request). The difference between the estimated odds ratios for the non-imputed cases and the imputed data indicated that multiple imputation corrected for an upward bias in the case estimates, assuming the data were missing at random.

Treatments after discharge

Three patients out of 4 (76.4%) underwent psychotherapy at the 3-month follow-up, while 3 out of 5 reported receiving psychotherapy at their 12-month follow-up (Supplementary table 8). About 1 patient out of 10 received drug monotherapy at their 3-month follow-up (8.2%) and 12-month follow-up (11.3%). Fourteen percent of the patients received a combined treatment at the 3-month follow-up, and 25% of the patients received a combined treatment at their 12-month follow-up. No significant difference between the treatment arms was found (3-month p=0.223; 12-month p=0.757).

Discussion

Brief and effective psychotherapy programs for use in short-term inpatient units are of great importance given the current clinical guidelines recommending combined treatment of moderate to severe depression. The present study aimed to examine the efficacy of an adjunctive, brief, and intensive psychodynamic psychotherapy compared to treatment-as-usual for inpatients during the acute phase of a major depressive episode. The results mostly supported the efficacy of inpatient brief psychodynamic psychotherapy. The depressed inpatients who received IBPP showed greater reductions in the severity of depressive

symptoms one month after intake compared with those who benefitted from TAU. The benefits of IBPP on depression severity were maintained 3 months and 12 months post-treatment. Significant differences were found in response rate but not in remission rate between the two groups one month after intake. The response and remission rates were superior in the IBPP group compared with the TAU group at 3 and 12 months. A majority of the patients received more than 10 sessions and only a few participants did not continue IPBB after discharge indicating a high acceptance of IBPP.

The effects of IBPP on depression severity were in the small to medium range and are comparable to those found in a meta-analysis summarizing the effects of the psychological treatment for depression in inpatients (Cuijpers et al., 2011). Our effect size at post-treatment (d=0.39) lies within the upper limit of the overall effect size of psychological treatments for depressed inpatients at post-treatment calculated by Cuijpers et al. (g=0.29, 95%CI 0.13-0.44). This relatively higher effect size may be due to the intensity of the inpatient treatment with IBPP. In one highest quality studies conducted to date, a more intensive treatment reported a higher effect size (d=0.62) favouring interpersonal psychotherapy (Schramm et al., 2007). Schramm et al. (Schramm et al., 2007) also showed that inpatient interpersonal psychotherapy (IPT) and pharmacotherapy outperformed pharmacotherapy and clinical management in terms of response rate (70% vs 51%) at discharge. A more recent study examining outcomes in inpatients receiving CBASP found that 71% of inpatients responded to CBASP and 40% of inpatients remitted (Brakemeier et al., 2015). The findings of the current study indicated a superiority of IBPP over TAU in terms of response rate (41% vs 23%) at discharge. The response rates at discharge after 12 sessions of IBPP were thus lower than those found with a 5-week course of inpatient interpersonal psychotherapy comprising 15 individual sessions and 8 group sessions (Schramm et al., 2007) and also lower than a 12-week course of CBASP comprising 2 weekly individual sessions and 2 weekly group sessions (Brakemeier et al., 2015). When considered together, those results may indicate the existence of a possible dose-response relationship to brief inpatient psychotherapy (Howard et al., 1986).

In contrast with Cuijper et al.'s (2011) meta-analysis, we found indications that the type of evaluation had an effect on the results. The self-report of symptom severity confirmed the findings obtained through independent ratings at 3 months post-treatment. Symptom reduction favoured IBPP, and the patients were more likely to have responded to IPBB than to TAU or to show a remission with IBPP than with TAU. However, no significant effect of IBPP was found at discharge. This difference between self-reports and independent ratings is

in line with previous studies showing differences in the effect sizes of psychotherapy with inpatients when measured with a self-report measure or when measured with an independent measure (Peeters et al., 2013; Stuart and Bowers, 1995). In the present study the self-report measure (QIDS-SR16) seemed less sensitive to change than the independent measure (MADRS). The MADRS has been proven to be more sensitive than the QIDS-SR16 in differentiating between depressed versus non-depressed outpatients (Bernstein et al., 2010). Our results may indicate that the MADRS is also more sensitive than the QIDS-SR16 to individual differences in severity of depression with inpatients. An alternative reason for this divergent evaluation of the depression severity between clinicians and patients might be that patients who report a greater severity of symptoms display more negativism, resentment and indirect hostility than those with a convergent evaluation (Castrogiovanni et al., 1989). Castrogiovanni et al. (1989) have suggested that those patients may not admit the effectiveness of external intervention because of their need to continue to ask for it. Once the intervention is terminated, negating the effect of the intervention loses its communicative purpose. Our results also re-affirm the value of multimodal assessments of depression severity when conducting of research on depressive disorders.

The fact that the effect of IBPP was stronger some 3 months after the end of the treatment was an unexpected result. It indicates a “delayed” effect of the active treatment. This “sleeper effect” may reflect the subjects’ implementation of the changes in self-awareness and in the insights gained during treatment (Crits-Christoph et al., 2003; Karyotaki et al., 2016; Maina et al., 2009; Muratori et al., 2003). It may also indicate an ongoing process of self-analysis they gained or experienced during IBPP. While unexpected, this result is consistent with previous meta-analyses showing that the benefits of psychodynamic psychotherapy increase with time (Abbass et al., 2014; Leichsenring et al., 2004). This sustained and delayed gain of inpatient psychotherapy also provides support to previous studies that suggest starting psychotherapy as early as possible (i.e., while in the hospital) (Miller et al., 2005; Miller et al., 1989). An early start may be more advantageous than delaying the initiation of psychotherapy until discharge. Within the follow-up period, patients underwent psychotherapy mostly with no significant difference between treatment arms. This finding supports the sustained effects of the inpatient treatment. The effects IBPP decreased 12 months after intake. This may be an early sign that the benefits of IBPP will not be maintained in the long-term. A single course of brief psychotherapy is very unlikely to induce long lasting immunity against relapse and the development of new symptoms of depression.

In addition, IBPP had a positive effect on patients’ global functioning 4 months after

intake as found by Schramm et al. (Schramm et al., 2007). This positive effect is important as functional impairment may persist even after the symptoms' resolution (Hirschfeld et al., 2000). Although the effect is neither immediate nor long lasting, this finding may still indicate that the effects of IBPP go beyond clinical effectiveness and can help patients to improve their functioning, thus meeting their wider needs. The global assessment of functioning rates incorporates information about psychiatric symptoms as well as social and occupational functioning. Because the global assessment of functioning is reported as a single score, it is unclear whether the delayed positive effect of IBPP on global functioning measures improvements in depression severity, in social functioning, or both.

Limitations

We need to acknowledge a number of limitations to this study. In order to increase the external validity of the trial, we limited the number of exclusion criteria. The sample is relatively heterogeneous in terms of diagnosis, with different subtypes of depression and comorbidity. As the heterogeneity increases the external validity and the generalizability of the study, we cannot rule out the influence of diagnosis or comorbid disorders on the treatment outcomes.

Also, the amount of therapeutic attention from the hospital staff in both treatments was not controlled for. We consider the amount of therapeutic attention unlikely to be a major factor: (1) mainly because, in inpatient settings, 3 sessions of psychotherapy added to the TAU only slightly increased the overall treatment dose that inpatients usually receives. This dose has been estimated to be 18 to 25 hours per week in an inpatient setting, similar to the setting of our study (Zeeck et al., 2015); (2) because in inpatient settings, there is a ceiling effect in terms of the amount of therapeutic contact among treatment groups (Schramm et al., 2007). Lastly, (3) the study used a RCT design. We did not find indications of any imbalances between the groups. Even though we cannot rule out possible imbalances, we are reasonably confident that the random allocation of patients controlled for the potential differences in the components used in both arms and that the effect measured was mostly the effect of IBPP. IBPP is a structured technique whereas some of the TAU interventions were less structured and specific. A future study comparing 2 structured treatments of similar duration added to the TAU to assess the effectiveness of inpatient psychodynamic psychotherapy can be advantageous.

The study had limited power to detect small to moderate effects, which prevented us from testing our hypotheses using subgroups. The dropout rate was higher in the IBBP arm than in the TAU arm. Dropout from the IBPP was defined as non-engagement in IBPP or as

early therapy discontinuation (before Session 3) whereas dropout from the TAU was defined as early hospital discharge (within the first week). Hence, the higher dropout rate in the IBPP arm of the study was mostly due to the fact that the IBPP is added to the usual treatment. Therefore, direct comparisons of the dropout rates seems not relevant. Relapse rates were not recorded in the follow-up assessments. This information should be collected in future research because it would provide important information on the distant efficacy of IBPP. The assessment timepoints did not allow the response curve to dynamic psychotherapy to be rated effectively throughout the year. Some intermediate points may be needed to identify when the effect starts decaying in future research. Finally, the therapists were external to the clinical unit, allowing them to adopt a clear psychodynamic attitude, as they were not responsible for any other part of the inpatient treatment. This mode of practice may not be common practice in other hospitals. Therefore, the generalizability of the data to other inpatient units, medical systems, or countries may be limited.

Conclusions

In summary, while limited by some factors, the results of this study suggest that there are substantial benefits to adding IBPP to usual care for treating major depression in a psychiatric hospital. The current findings support recent propositions on the importance and feasibility of more intensive psychological treatment for depressed inpatients (Porter et al., 2016). The significance of the findings goes beyond the specific intervention and the characteristics of the medical system used to implement the study. Despite the great diversity in the structure of inpatient facilities worldwide, some issues are shared across countries such as the difficulty in forming therapeutic relationships and patients preferences for psychological approaches (Lelliott and Quirk, 2004). In the post-institutional era, psychiatric hospitals face strong economic incentives to shorten lengths of stay while also having to maintain good quality care (Craig, 2016; Cresswell et al., 2014). Implementing new therapeutic regimes such as brief psychotherapies may help depressed inpatients to find meaning in their current unhappiness and new tracks out of it. An inpatient stay represents an opportunity to deliver therapy in an effort to achieve the fullest and earliest possible recovery. IBPP may also be an opportunity to provide appropriate training and supervision to clinical staff who work in very demanding conditions. Future studies should investigate whether subgroups of depressed inpatients may benefit more from add-on IBPP than others.

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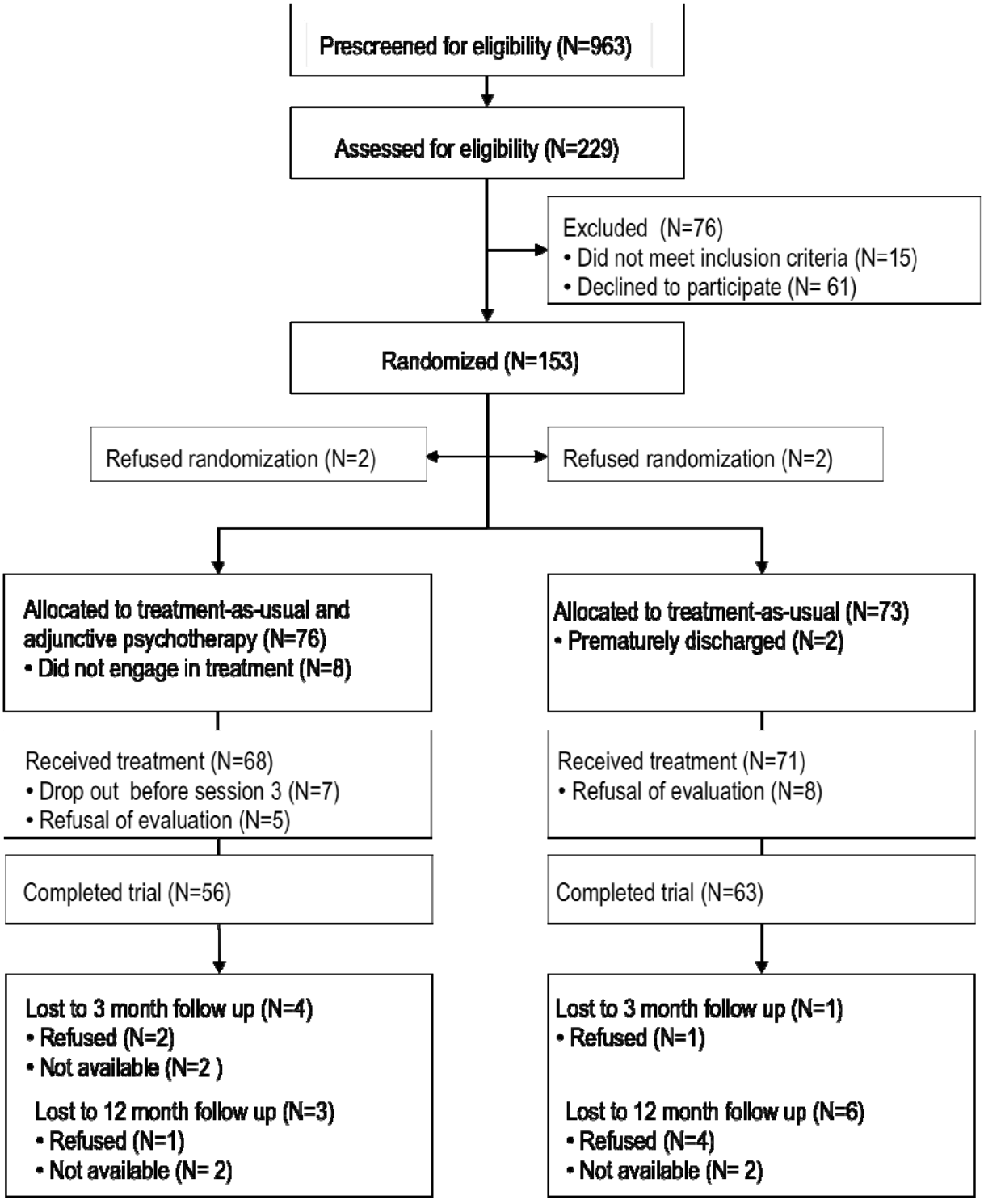

Figure 1. CONSORT flow diagram

Table 1 Baseline demographics and clinical characteristics

	Treatment IBPP	**Control group TAU**	**Total**	
	Mean (SD) n (%)	**Mean (SD) n (%)**	**Mean (SD) n (%)**	***p* val.**
	(n=76)*	(n=73)*	(N=149)*	
Age	43.6 (10.2)	43 (10.7)	43.2 (10.4)	0.688
Gender				
Male	24 (31.6)	17 (23.3)	41 (27.5)	
Female	52 (68.4)	56 (76.7)	108 (72.5)	0.257
Family Status				
Single	15 (23.4)	19 (30.2)	34 (26.8)	
Married	24 (37.5)	17 (27.0)	41 (32.3)	
Divorced/widow	25 (39.1)	27 (42.9)	52 (40.9)	0.420
Education (years)	10.6 (3.0)	11.1 (2.7)	10.9 (2.8)	0.348
Employed	32 (43.8)	31 (44.9)	63 (42.3)	0.896
Early onset	23 (34.9)	18 (29.0)	41 (27.5)	0.481
Age at onset	29.7 (13.4)	31.1 (12.5)	30.4 (12.9)	0.514
Length of stay (days)	38.1 (34.9)	35.0 (30.7)	36.6 (24.5)	0.567
Recurrence	28 (37.3)	32 (45.7)	62 (41.6)	0.306
Chronicity	39 (52.0)	27 (38.6)	66 (44.3)	0.105
History of suicide attempts	34 (55.7)	33 (60.0)	67 (57.8)	0.643
Comorbidity				
Axis I	64 (94.1)	56 (87.5)	120 (90.9)	0.233
Axis II	27 (37.5)	25 (37.3)	52 (37.4)	0.982
Antidepressant	50 (71.4)	57 (81.4)	107 (74.8)	0.646
QIDS-SR	16.76 (4.41)	17.33 (3.96)	17.04 (4.21)	0.414
MADRS	29.42 (6.73)	30.88 (6.69)	30.13 (6.72)	0.187
GAF	44.04 (11.13)	42.69 (9.71)	43.39 (10.45)	0.436

*N and n can vary due to missing data

TAU = Treatment-as-usual; IBPP = Inpatient Brief Psychodynamic Psychotherapy; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Rating; MADRS = Montgomery-Asberg Depression Rating Scale; GAF = Global Assessment of Functioning

Table 2 Time and treatment effect on depression severity and global functioning using multiple imputation (N=149, Effect size, 95%CI)

	Time effect			IBPP effect (control vs treatment)		
Scales	**Post-treatment**	**3 months**	**12 months**	**Post-treatment**	**3 months**	**12 months**
MADRS	0.36	0.27	0.34	0.39	0.46	0.32
	(0.21, 0.50)*	(0.11, 0.43)*	(0.20, 0.49)*	(0.06, 0.71)*	(0.14, 0.78)*	(0.01, 0.64)*
QIDS-SR	0.45	0.32	0.39	0.19	0.47	0.24
	(0.30, 0.59)*	(0.17. 0.48)*	(0.24, 0.54)*	(-0.13, 0.50)	(0.14, 0.79)*	(-0.08. 0.56)
GAF	0.36	0.15	0.13	-0.24	-0.52	-0.28
	(0.20, 0.51)*	(-0.02, 0.31)	(-0.04, 0.29)	(-0.56, 0.08)	(-0.84, -0.19)*	(-0.60, 0.04)

Note: QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Rating; MADRS = Montgomery–Asberg Depression Rating Scale; GAF = Global Assessment of Functioning; IBPP = Inpatient Brief Psychodynamic Psychotherapy;

IBPP effect comprises the effect of treatment and the effect of the interaction between the treatment and the group (F-test: MADRS, $p = 0.004$, QIDS, $p = 0.009$; GAF, p = 0.083)

Pearson's r for time effect, $r = 0.10$ small, $r = 0.30$ medium, $r = 0.50$ large

Cohen's d for time x IBPP effect, $d = 0.20$ small, $d = 0.50$ medium, $d = 0.80$ large

*$p < 0.05$

Using 50 imputed data sets

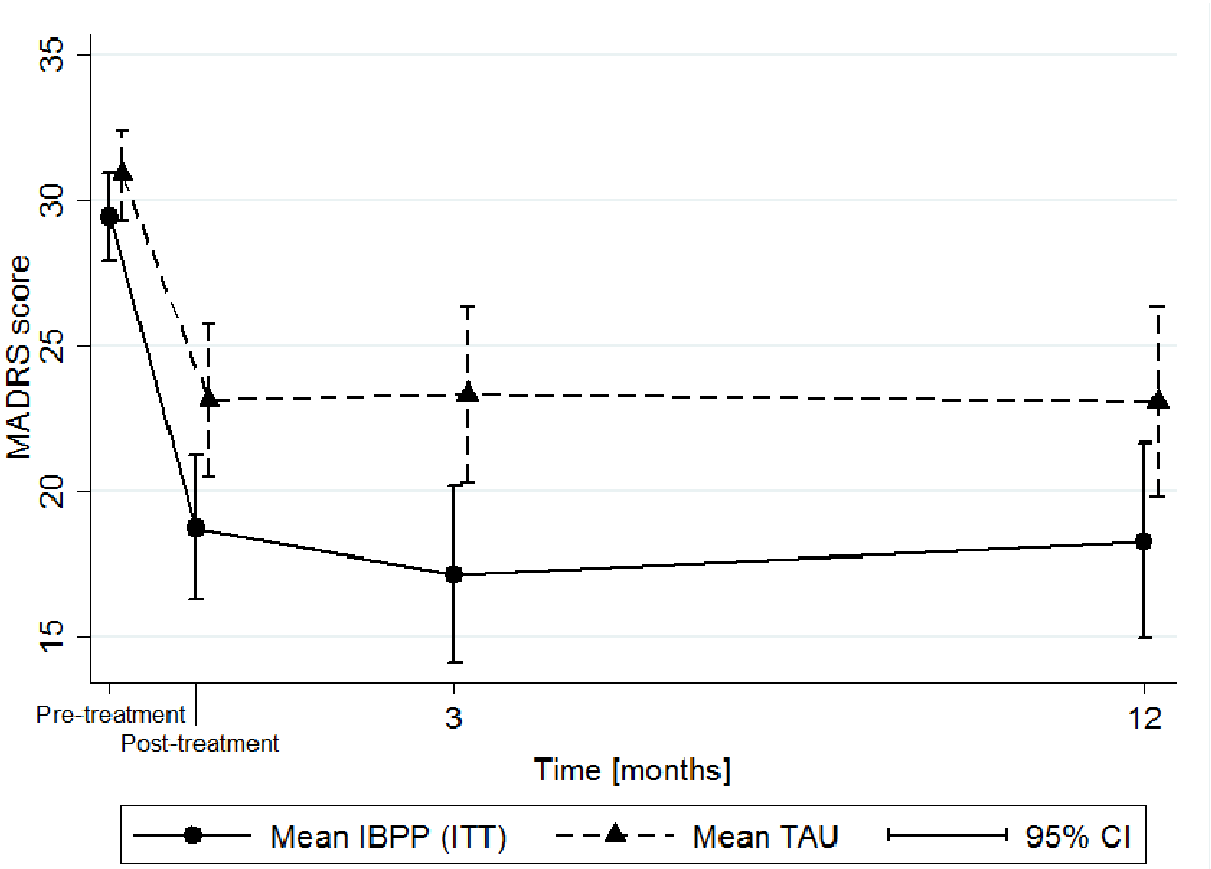

Figure 2 Depression severity trajectories for TAU and adjunctive IBPP groups
TAU = Treatment-as-usual; IBPP = Inpatient Brief Psychodynamic Psychotherapy; MADRS = Montgomery–Asberg Depression Rating Scale

Table 3 Individual Response and Remission using multiple imputation (N=149)

Scales			**IBPP (%)**	**TAU (%)**	**OR**	**95%CI**	**p-value**
MADRS	Response	Post-treatment	*41.0*	*22.6*	2.69	(1.18 – 6.11)	0.018
		3 months	*52.6*	*27.4*	3.39	(1.51 - 7.61)	0.003
		12 months	*48.7*	*34.1*	2.26	(1.02 - 4.97)	0.043
	Remission	Post-treatment	*18.3*	*10.4*	2.28	(0.73 - 7.09)	0.154
		3 months	*32.3*	*13.8*	3.48	(1.32 - 9.17)	0.012
		12 months	*31.7*	*14.3*	3.75	(1.36 - 10.30)	0.010
QIDS	Response	Post-treatment	*20.5*	*21.1*	1.03	(0.42 - 2.50)	0.953
		3 months	*43.7*	*19.4*	3.76	(1.56 - 9.06)	0.003
		12 months	*36.3*	*27.4*	1.67	(0.75 - 2.71)	0.211
	Remission	Post-treatment	*10.6*	*8.9*	1.22	(0.37 - 4.10)	0.742
		3 months	*30.3*	*12.0*	3.86	(1.36 - 10.91)	0.011
		12 months	*25.3*	*15.2*	2.11	(0.83 - 5.33)	0.116

Note: TAU = Treatment-as-usual; IBPP = Inpatient Brief Psychodynamic Psychotherapy; QIDS-SR = Quick Inventory of Depressive Symptomatology–Self Rating; MADRS = Montgomery–Asberg Depression Rating Scale

Adjusted for sex, age, recurrence, chronicity and severity at baseline

Using 50 imputed data sets

Clinical Vignette

April is a 35 years old patient with a diagnosis of recurrent depressive disorder who was hospitalized for the first time due to a third major depressive episode. During her first encounter with the therapist she has a neat presentation; she is smiling but she looks fearful. She states that this is her first time confiding and connecting to the verbal and physical abuse she suffered from her grandmother during her childhood and adolescence. “All of my grandmother’s violence is in me,” she says. She continues with the context of her actual crisis: her separation from a man with whom she had a stormy and violent relationship. This painful separation has coincided with her wish for a child.

During the middle sessions, April and the therapist elaborate further on her separation. She evokes childhood memories and talks about her dependence on others, as well as of her fear of being manipulated and abandoned. The sessions also allude to her ambivalence about relationships, her confusion between anger and sadness, and her rivalry with her mother, from which she cannot distance herself. She sees herself in her mother’s deformed body giving birth to a child in a dream. The therapist and April can thus share and elaborate upon insights into her violence and her wish to be simultaneously a small victim and a skillful manipulator. Being a mother worries her, as does her jealousy.

The work on therapy termination raises the issue of April’s working life. The therapist mentions April’s renewed interest about working, as did her mother. During the next session, April shows a new tattoo to the therapist, which appears to have been particularly painful to get. The therapist identifies himself as an aggressor and returns to the violence that she may have felt coming from him during the previous session. April makes the link with her mother, who did not see her bruises. The acknowledgement of that violence during the separation phase of the therapy seems to relieve her. During the last session, April states that she can “see things differently with a lot of tolerance.” She has contacted a psychiatrist and feels capable of taking responsibility for the treatment.

At the end of the therapy, there is a clinically significant improvement in April’s symptomatology (MADRS and QIDS). At the 3- and 12-month follow-ups, April’s symptoms are in remission.