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What Is the Best Sequential Treatment Strategy in the Treatment of Depression? Adding Pharmacotherapy to Psychotherapy or Vice Versa?

Jack Dekker[a, d] Henricus L. Van[a] Mariëlle Hendriksen[a] Jurrijn Koelen[b]
Robert A. Schoevers[c] S. Kool[a] G. van Aalst[a] Jaap Peen[a]

[a]Arkin Mental Health Institute, Amsterdam, [b]Altrecht Psychosomatic Medicine, Utrecht, [c]Department of Psychiatry, University Medical Centre, Groningen, and [d]Department of Clinical Psychology, Faculty of Psychology and Education, Vrije Universiteit, Amsterdam, The Netherlands

Key Words
Depression · Psychodynamic psychotherapy · Pharmacotherapy · Sequential treatment strategy

Abstract
Background: Insufficient response to monotreatment for depression is a common phenomenon in clinical practice. Even so, evidence indicating how to proceed in such cases is sparse. ***Methods:*** This study looks at the second phase of a sequential treatment algorithm, in which 103 outpatients with moderately severe depression were initially randomized to either short-term supportive psychodynamic therapy (PDT) or antidepressants. Patients who reported less than 30% symptom improvement after 8 weeks were offered combined treatment. Outcome measures were the Hamilton Depression Rating Scale (HAM-D), the Clinical Global Impression of Severity and Improvement, the SCL-90 depression subscale and the EuroQOL questionnaire. ***Results:*** Despite being nonresponsive, about 40% of patients preferred to continue with monotherapy. At treatment termination, patients initially randomized to PDT had improved more than those initially receiving antidepressants, as indicated by the HAM-D and the EuroQOL, independently of whether the addition was accepted or not. ***Conclusions:*** Starting with psychotherapy may be preferable in mildly and moderately depressed outpatients. For patients who receive either PDT or antidepressants, combined therapy after early nonresponse seems to be helpful. Nevertheless, this sequential strategy is not always preferred by patients.

Introduction

The different forms of psychotherapy and pharmacotherapy appear to be equally effective in the acute treatment of moderate-to-severe depression [1–4]. The combination of psychotherapy and pharmacotherapy seems to be more beneficial than pharmacotherapy alone [5–8], especially in severe depression. However, the advantage of combined treatment over monopsychotherapy is less clear-cut [9–12].

It is not unusual in clinical practice to start with monotreatment: there are cost-efficacy considerations, not all treatment options are available, there are possible side effects and adherence is higher in monotherapies [13, 14]. A sequential strategy may be used in patients who fail to respond. Segal et al. [13] and Fava et al. [14, 15] recommend sequencing pharmacotherapy and psychotherapy

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Jack Dekker
Arkin Institute for Mental Health Care Amsterdam
PO Box 75848
NL–1070 AV Amsterdam (The Netherlands)
E-Mail jack.dekker@mentrum.nl

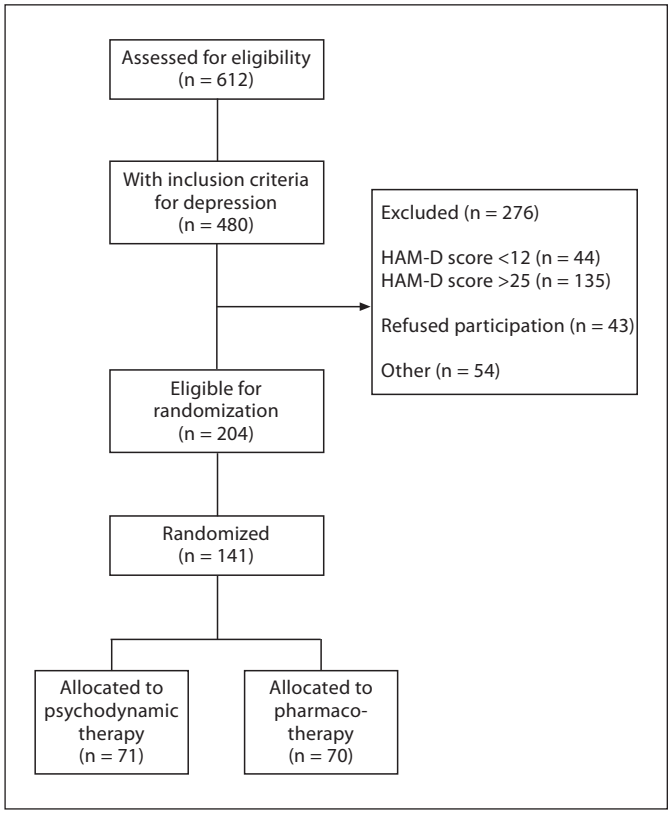

Fig. 1. Flow of participants through the first stages of the randomized trial.

for depression, especially for more severely depressed patients [13], but sequential strategies of this kind have not often been studied. We are aware of only one study (looking at women with recurrent depression [16]) in which pharmacotherapy was prescribed after unsuccessful psychotherapy. This appeared to be slightly more effective than combined therapy from the start [16]. The reverse sequence – the addition of psychotherapy after nonresponse to pharmacotherapy for depression – has been studied more frequently [17–27]. In all of these studies, the psychotherapy was a form of cognitive behavior therapy and it was mainly added to prevent relapse after partially or fully successful pharmacotherapy.

The aim of the present study was to determine which sequence is preferable for the acute treatment of depression: starting with psychodynamic therapy (PDT) or with pharmacotherapy. Although PDT is effective in depression [28–35], it has never been studied in a sequential treatment design. This study started with a randomized clinical trial of 8 weeks, making a direct comparison between antidepressants (AD) and short-term, supportive PDT. In a previous article [36], we reported slightly better results for AD by week 4. This benefit had almost disappeared by week 8. This article covers the entire course of treatment and focuses on the differential efficacy of the treatment strategies after 24 weeks. At 8 weeks, all patients with less than a 30% decrease in symptoms were offered combined therapy for an additional period of 16 weeks. Nonresponsive patients receiving AD were therefore offered complementary PDT, while nonresponsive patients receiving PDT were offered complementary AD.

The aim of this article is to explore the acceptability, feasibility and efficacy of the sequential treatment strategies in cases of poor response after 8 weeks of treatment. Secondly, we hoped to determine which of the sequential strategies would be preferable: complementary AD after PDT or complementary PDT after AD.

Methods

Subjects

The study sample comprised all consecutive patients newly registered over a period of 3 years at two outpatient clinics of Mentrum Mental Health Care, a large psychiatric academic hospital with extensive outpatient facilities in the city of Amsterdam. The inclusion criteria were: age between 18 and 65 years, DSM-IV-defined Depressive Episode with or without dysthymia (using the CIDI), a 17-item Hamilton Depression Rating Scale (HAM-D) [37] baseline score between 14 and 26 points, and written informed consent. The exclusion criteria were: bipolar disorder, drug abuse, psychotic symptoms, serious communicative problem (language, for example) or physical restrictions (patient due to leave the country soon, for example) precluding participation, the necessity of immediate hospitalization or day treatment, and contraindication for ADs (inability to stop using present psychotropic medication, or pregnancy).

Study Design

Figure 1 shows a flow diagram for the study population. During the study period 480 patients met the inclusion criteria for depression as determined by the regular intake procedure of the departments and confirmed with the CIDI. We excluded 276 patients for the following reasons: HAM-D score <12 (n = 44), HAM-D score >25 (n = 135), and refusal to participate (n = 43) or other reasons (n = 54). In addition, another 63 patients dropped out during intake and before the randomization procedure. The reasons here were organizational: the overly long absence of the patients due to, for example, a holiday. In conclusion, 71 patients were allocated to PDT and 72 to AD.

After randomization, 8 patients (n = 1 in the PDT arm and n = 7 in the AD arm) refused the randomized intervention and decided to follow their own preferred course of treatment [36, 38]. Fifteen patients (n = 3 in the PDT arm and n = 12 in the AD arm) refused all treatment and 15 patients (n = 8 in the PDT arm and n = 7 in the AD arm) did not show up.

Finally, 103 patients were included in the per protocol analysis (these were the patients who actually started treatment): 59 to the psychotherapy group and 44 to the pharmacotherapy group.

After 8 weeks of treatment, a sequential strategy was implemented. Insufficient response was defined as <30% HAM-D reduction. This cut-off was based on clinical consensus. On the one hand, it reflects slightly more improvement then the usual operationalization of <25% decrease for complete nonresponse [39–42]. On the other hand, it reflects a realistic approach to the expected change in the first phase of psychotherapy. These nonresponsive patients were offered the complementary treatment: additional PDT or AD for the remainder of the research period, i.e. until week 24. All other patients continued monotreatment until week 24.

Treatment

Pharmacotherapy. Pharmacotherapy was provided in accordance with an AD protocol. All patients started with the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine (75 mg/day). Depending on clinical response and tolerability, the dose of venlafaxine could be titrated up to a maximum of 225 mg/day. In cases of intolerance (according to both psychiatrist and patient), the first-choice AD could be replaced by citalopram (maximum dose 60 mg/day) or nortriptyline (maximum dose 150 mg/day). Patients had four fortnightly appointments with the pharmacotherapist in the first 2 months and appointments once a month in the second phase of treatment. Except for the first visit, all appointments lasted a maximum of 20 min, during which adequate clinical management was provided. All pharmacotherapists, either psychiatrists or residents, were experienced in the pharmacological treatment of depression. Residents were supervised regularly by psychiatrists.

Psychotherapy. The psychotherapy consisted of sixteen sessions of short-term, supportive PDT. A range of trials and studies have demonstrated its effectiveness in the treatment of depression [7, 9, 38, 42–52]. The first eight sessions took place weekly, the last eight fortnightly. PDT is a manual-based approach focusing on the affective, behavioral and cognitive aspects of relationships from a psychodynamic point of view [53, 54]. Initially, these areas are discussed from an interpersonal perspective, in other words the actual relationship with others. Subsequently, the therapist proceeds to an intrapersonal perspective by focusing on the internalizations of former relationships that are relevant to the vulnerability to depression.

Depending on the focus of therapy and patients' capacities, the therapists may choose more supportive interventions – such as encouraging adaptive coping mechanisms, guilt-reducing thoughts or giving praise – or interventions for enhancing insight such as exploring affects or confrontation. Manifestations of defense mechanisms and transference are recognized and discussed if appropriate but not interpreted in depth. This means that the therapy is psychodynamic in terms of the intended therapeutic process and supportive in terms of the therapist's basic attitude. It differs from IPT by using psychodynamic concepts and because of the focus on the interdependence of actual relationships and intrapersonal representations.

PDT is used regularly by the participating outpatient departments to treat depressed patients. Therapists were trained in the principles of PDT (using the SPSP manual [53, 54]) in a 15-hour course, and were required to have completed one or more supervised therapies (depending on previous psychotherapeutic experience) before providing treatment in the research setting. Therapist competence in PDT was evaluated by one of the supervisors before the therapists were allowed to participate in the current study. The two study supervisors were psychoanalytic psychotherapists registered with the Dutch Association of Psychoanalytic Psychotherapy. Thirteen therapists (8 female and 5 male) participated in this trial. They were either psychiatrists (n = 4), advanced residents in psychiatry (n = 3), psychotherapists (n = 3) or advanced psychotherapy trainees (n = 3). During the research project, there was weekly supervision for the residents and trainees. The other therapists met twice a week for peer supervision, together with one of the study supervisors. Supervision of integrity was based on audio-taped material of sessions and focused on the course of depressive symptoms, the optimization of the therapeutic process, and the technical quality of interventions. The supervisors also monitored adherence to the psychotherapy manual, although this was not formally assessed.

Primary and Secondary Outcome Measures

The primary instrument was the 17-item HAM-D [37]. HAM-D data were provided by independent observers (three research fellows who were blind to the treatment condition). Data were gathered using a semistructured interview [55, 56]. The reliability of observer assessments was assessed prior to participation in the study. During the study, the research assistants discussed their audiotaped assessments monthly with an experienced psychiatrist.

There were several secondary outcome measures. The Clinical Global Impression of severity and improvement (CGI-S, CGI-I [57]) was used. CGI data were provided by the treating clinicians. In addition, the depression subscale of the Ninety Symptom Checklist (SCL-D) [58] was used as a self-report measure. Finally, the EuroQOL questionnaire, an instrument developed for evaluating health and health care [59], was used to measure health status. For pragmatic reasons, only item 5 was used. This is a self-rated 10-point visual analogue scale asking the patient: 'How good or bad is your general health status today?' In short, our efficacy assessments were based on data from three sources: the treating clinicians, the patients and independent observers.

The second phase of the trial included assessments at week 8, week 16 and week 24. Efficacy was expressed as differences in mean scores. HAM-D response was defined as a 50% symptom reduction. The criterion for complementary treatment was a reduction of less than 30% on the HAM-D and it was used at week 8 only.

Psychotherapy patients who completed fewer than five therapy sessions in the first 8 weeks or who terminated participation between weeks 8 and 24 were considered to be dropouts, whatever the reasons. AD drop-out was defined as self-reported noncompliance with the medication regime or no-shows at follow-up appointments with the pharmacotherapist prior to week 16.

Statistical Analysis

Pearson χ^2 calculations were used to compare baseline characteristics, refusal rates, drop-out rates and success rates between therapy conditions. ANOVA was used to compare the baseline measurements of the two groups.

ANCOVA analyses were used to test between-group differences in terms of means, including baseline measures, and pos-

Table 1. Patient characteristics (per protocol sample)

	Psycho-therapy (n = 59, %)	Pharmaco-therapy (n = 44, %)	Total (n = 103, %)
Sex			
Male	25.4	27.3	26.2
Female	74.6	72.7	73.8
Age			
20–29 years	32.2	15.9	25.2
30–39 years	35.6	43.2	38.8
40–49 years	16.9	27.3	21.4
50–60 years	15.3	13.6	14.6
Education level			
Low	24.1	38.1	30.2
Intermediate	50.0	42.9	46.9
High	25.9	19.0	22.9
Patient was on medication 3 months prior to admission[1]			
Yes	30.4	51.2	39.4
No	69.6	48.8	60.6
Psychiatric treatment for present episode			
Treated	43.6	43.2	43.5
Not treated	56.4	56.8	56.5
Duration of present episode			
<1 year	48.2	44.1	46.7
1–2 years	23.2	17.6	21.1
>2 years	28.6	38.2	32.2
Depressive episodes in past 5 years			
0	48.2	47.6	48.0
1	41.1	42.9	41.8
2	5.4	2.4	4.1
≥3	5.4	7.1	6.1
HAM-D score			
Mean	20.4	19.8	20.1
SD	3.8	3.7	3.7
Median	20.0	20.0	20.0
CGI-S score			
Mean	4.4	4.1	4.3
SD	0.7	0.7	0.7
Median	4.0	4.0	4.0
SCL-D score			
Mean	51.8	51.5	51.7
SD	10.0	11.6	10.6
Median	51.5	53.0	52.5

[1] $\chi^2 = 4.41$; p = 0.036.

sible differences in baseline characteristics between therapy conditions as covariates.

Data analyses were performed on a per protocol sample and on an observed cases sample. The per protocol sample included all the patients who started treatment. last observation carried forward (LOCF) was applied to the per protocol sample for missing data. The observed cases sample included only the observed data for all patients who completed treatment.

A general linear model repeated-measures analysis (GLM procedure in SPSS) was conducted to test the efficacy of the two sequential strategies. Time, initial strategy (PDT or AD), complementary therapy (in case of nonresponse), and the interaction between treatment group and complementary therapy were entered as predictors of the mean HAM-D score at week 24. Possible differences between baseline characteristics in the therapy conditions were also entered.

The power of the trial was about 0.7 for 103 patients to determine a moderate Cohen effect size of 0.5 in favor of the PDT strategy.

Results

Demographics

Table 1 shows the demographic and clinical characteristics for the per protocol patient sample. No differences were found between the therapy groups, except for the use of medication in the three months preceding admission. In the pharmacotherapy group, significantly ($\chi^2 = 4.41$; d.f. = 1; p = 0.04) more patients had been using medication prior to intake at our outpatient clinic (51.2 vs. 30.4%).

Phase 1 (Weeks 0–8)

By week 8, sixteen (36.4%) of the randomized pharmacotherapy patients (n = 44) achieved a reduction of more than 30%. Eleven of the 59 randomized patients in the psychotherapy group (18.6%) achieved a reduction of more than 30%. This difference was significant ($\chi^2 = 4.09$; d.f. = 1; p = 0.043). In the analyses of the mean severity scores we found that, by week 8, the AD group was significantly better off than the PDT group on the HAM-D and the SCL-D depression subscale (both in the per protocol and observed cases samples) (table 2). The other assessments for more general clinical functioning, i.e. CGI and EuroQOL, did not show any significant improvement.

The patients with a reduction of more than 30% continued with the same monotreatment. All nonresponsive patients were offered the option of moving on to the combination therapy. Not all nonresponders accepted the additional therapy. Of the 29 nonresponsive patients in the PDT condition, 17 (58.6%) started with the additional therapy. Twelve of the 18 patients (66.7%) in the AD condition did so. The remaining patients continued monotreatment as scheduled. The percentages for the acceptance of additional therapy proved (with χ^2 testing) to be about the same in both groups.

Attrition Rates

By 8 weeks, no significant differences in attrition rates were found (32.2% (n = 19) in the allotted psychotherapy

Table 2. Mean scores for the four outcome measures in the two study samples, with between-group test results, controlling for baseline differences (ANCOVA)

	Psychotherapy			Pharmacotherapy			Total			F	p
	mean	SD	n	mean	SD	n	mean	SD	n		
Per protocol sample											
HAM-D											
Week 0	20.39	3.78	59	19.82	3.68	44	20.15	3.73	103	0.376	0.541
Week 8	18.39	6.51	59	15.59	6.45	44	17.19	6.60	103	4.398	**0.039**
Week 16	15.83	7.41	59	16.02	6.93	44	15.91	7.17	103	0.066	0.797
Week 24	13.34	8.08	59	16.07	7.58	44	14.50	7.95	103	3.572	*0.062*
CGI-S											
Week 0	4.42	0.74	55	4.14	0.74	43	4.30	0.75	98	2.667	0.106
Week 8	3.60	1.07	57	3.32	0.91	44	3.48	1.01	101	1.822	0.180
Week 16	3.05	1.25	57	3.07	1.00	44	3.06	1.14	101	0.154	0.696
Week 24	2.65	1.34	57	3.00	1.33	44	2.80	1.34	101	2.663	0.106
CGI-I											
Week 0											
Week 8	3.25	0.91	57	3.05	0.94	42	3.16	0.92	99	1.576	0.212
Week 16	2.91	1.15	57	2.69	0.84	42	2.82	1.03	99	1.928	0.168
Week 24	2.63	1.17	57	2.71	1.15	42	2.67	1.16	99	0.172	0.680
SCL-D											
Week 0	51.80	9.96	56	51.53	11.59	38	51.69	10.59	94	0.002	0.961
Week 8	46.64	12.92	58	41.88	12.62	42	44.64	12.95	100	11.410	**0.001**
Week 16	41.22	14.25	58	39.84	13.28	43	40.63	13.79	101	1.110	0.295
Week 24	37.24	14.74	58	39.60	13.70	43	38.25	14.29	101	0.288	0.593
EuroQOL											
Week 0	5.18	1.42	45	4.87	1.55	30	5.05	1.47	75	0.518	0.474
Week 8	5.44	1.50	55	5.70	1.74	40	5.55	1.60	95	0.434	0.512
Week 16	5.95	1.65	55	5.59	1.82	41	5.79	1.72	96	0.606	0.439
Week 24	6.36	1.66	55	5.33	2.17	42	5.92	1.96	97	8.469	**0.005**
Observed cases sample											
HAM-D											
Week 0	20.33	3.87	59	19.82	3.73	44	20.15	3.73	103	0.376	0.541
Week 8	18.04	6.98	48	14.56	6.07	39	16.48	6.78	87	4.450	**0.038**
Week 16	12.89	7.16	37	14.97	7.06	30	13.82	7.14	67	1.544	0.219
Week 24	9.84	6.81	37	15.45	8.05	31	12.40	7.86	68	11.498	**0.001**
CGI-S											
Week 0	4.42	0.74	55	4.14	0.74	43	4.30	0.75	98	2.667	0.106
Week 8	3.55	1.04	42	3.08	0.84	26	3.37	0.99	68	2.354	0.130
Week 16	2.69	1.17	36	2.74	0.99	19	2.71	1.10	55	0.052	0.821
Week 24	2.19	1.11	31	2.95	1.54	19	2.48	1.33	50	4.330	**0.043**
CGI-I											
Week 0											
Week 8	3.24	0.91	42	3.00	1.06	26	3.15	0.97	68	0.664	0.418
Week 16	2.75	1.25	36	2.42	0.77	19	2.64	1.11	55	1.707	0.197
Week 24	2.20	1.06	30	2.63	1.30	19	2.37	1.17	49	1.647	0.206
SCL-D											
Week 0	51.80	9.96	56	51.53	11.59	38	51.69	10.59	94	0.002	0.961
Week 8	43.28	12.37	39	39.66	11.96	32	41.65	12.23	71	6.629	**0.012**
Week 16	35.55	14.24	31	37.79	11.50	28	36.61	12.95	59	0.310	0.580
Week 24	31.27	12.14	30	38.12	13.47	26	34.45	13.11	56	3.648	*0.062*
EuroQOL											
Week 0	5.18	1.42	45	4.87	1.55	30	5.05	1.47	75	0.518	0.474
Week 8	5.58	1.58	40	5.79	1.87	28	5.66	1.70	68	0.010	0.922
Week 16	6.45	1.67	31	5.48	1.72	27	6.00	1.75	58	4.832	**0.034**
Week 24	6.80	1.57	35	5.39	2.41	23	6.24	2.05	58	13.491	**0.001**

Italics = $p < 0.1$; bold = $p < 0.05$.

condition and 22.7% (n = 10) in the allotted pharmacotherapy condition). Between weeks 8 and 24, one patient in the PDT group dropped out of therapy at week 12 and 4 dropped out at week 16 (5 patients in total). In the AD group, 4 patients terminated their treatment at week 12 and 2 patients did so at week 16 (6 patients in total). These percentages (12% in PDT and 18% in AD) were not significantly different. It can therefore be seen that drop-out mainly occurred in the first phase. Over the total research period, 40 out of 103 patients (38.7%) dropped out from the treatment groups taken together.

Overall Efficacy of the Sequential Treatment Algorithms

Table 2 presents the efficacy results during the total treatment period expressed as mean scores in the per protocol sample and the observed cases sample (between-group differences were tested using ANCOVA to check for baseline differences).

By week 8, the AD group was better off than the PDT group. However, after week 8, the pattern of results was reversed. By week 16, the two groups had about the same scores in almost all respects, with the exception of quality of life: the PDT group had significantly higher quality of life scores. The patients who started with PDT in the per protocol sample had better results at the end of treatment than those who started with AD (according to the SCL-D and the EuroQOL). Furthermore, a trend was found with respect to the HAM-D. In the observed cases sample, all but one of the four measures significantly favored patients who started with PDT. There was a trend with respect to the SCL-D.

We used a GLM repeated measures analysis to test the influence of the independent variables – time, initial strategy, the additional treatment, and the interaction of initial strategy and the additional treatment – on the severity of symptoms during the treatment period (the dependent variables in the GLM analysis were the scores for HAM-D, CGI, SCL and EuroQOL at T0, T8, T16 and T24). Table 3 sets out the statistical parameters (the Greenhouse-Geisser F and p) for the independent variables in the analysis.

In the per protocol and observed cases samples, the sample time and initial strategy had a significant influence on the decline of severity. Symptom severity was reduced over the research period. At the end of treatment, the PDT-first strategy had produced significantly better results (using almost all measures) than the AD-first strategy.

Additional treatment after week 8 resulted in a greater reduction of the HAM-D scores than no additional treatment in both samples. In the per protocol sample, additional treatment also produced better results as reported by the patients and as assessed by the therapists.

The interaction of initial strategy and additional treatment was only significant in the per protocol sample for the CGI measures. The power for testing time (as a factor), initial strategy and additional treatment factors varied from 0.70 to 0.99. The power for testing the interaction variable was too low in almost all cases (varying from 0.06 to 0.5), except in the cases of the significant interactions in the per protocol sample: power for testing CGI-S 0.93, and 0.63 for testing CGI-I.

To illustrate the slopes in the four groups, online suppl. fig. 1 (www.karger.com/doi/10.1159/000341177) shows the mean scores on HAM-D for the four groups during the treatment (from the per protocol samples).

Almost all the measures showed the same pattern. In the beginning, patients using AD improved more, but PDT led to better results in the end.

Secondary Analyses

In the analyses above, we allocated all the patients to four subgroups: ADT or PDT patients with or without addition. Another approach to making subgroups in this complex study is to divide all the patients into three subsamples: responders (without addition), nonresponders with addition and nonresponders without addition. We used GLM to test the possible differences in outcome between the two initial strategies (AD or PDT) in these three subsamples. Because of the smaller sample sizes, we also state the observed power here.

In the secondary GLM subgroup analyses (of the HAM-D scores at T0, T8, T16 and T24) for responders only, the interaction effect was a trend ($F = 2.46$; $p = 0.079$; observed power = 0.54). The AD responders did not improve significantly any further between weeks 8 and 24 (mean T0: 19.21; mean T8: 9.95; mean T16: 13.11; mean T24: 12.95). This contrasted with the PDT responders (mean T0: 18.31; mean T8: 9.46; mean T16: 9.31; mean T24: 6.77).

In similar secondary GLM subgroup analyses of the group of nonresponders who refused additional therapy, we also found an interaction effect that was a trend ($F = 2.37$; $p = 0.10$; observed power = 0.46). The AD nonresponders who refused additional PDT did not improve significantly between weeks 8 and 24 (mean T0: 21.00; mean T8: 20.92; mean T16: 20.58; mean T24: 21.75). This contrasted with the nonresponsive PDT patients who refused additional AD. There was a trend of improvement between week 8 and week 24 (mean T0: 20.81; mean T8: 20.46; mean T16: 19.35; mean T24: 18.12).

Table 3. Influence of time, intervention, addition, interaction intervention and addition on symptoms during treatment

Independent variables	Dependent variables									
	HAM-D		SCL-D		CGI-S		CGI-I		EuroQOL	
	F	p	F	p	F	p	F	p	F	p
Per protocol sample										
Time	20.29	***0.000***	23.55	***0.000***	39.65	***0.000***	13.78	***0.000***	3.90	***0.014***
Intervention AD or PDT	5.61	***0.002***	4.02	***0.016***	7.39	***0.000***	4.00	***0.020***	3.25	***0.030***
Addition	10.16	***0.000***	3.72	***0.021***	2.10	0.115	6.11	***0.003***	1.48	0.225
Intervention * addition	0.86	0.449	0.80	0.464	5.36	***0.003***	3.37	***0.037***	0.89	0.434
Observed cases sample										
Time	19.89	***0.000***	19.74	***0.000***	11.23	***0.000***	2.47	*0.096*	4.81	***0.008***
Intervention AD or PDT	5.46	***0.003***	2.12	0.111	10.48	***0.000***	3.90	***0.028***	4.14	***0.015***
Addition	10.50	***0.000***	1.83	0.156	1.84	0.157	0.12	0.874	1.05	0.367
Intervention * addition	0.05	0.970	0.05	0.976	2.02	0.130	0.46	0.621	1.20	0.312

Italics = $p < 0.1$; bold = $p < 0.05$.

In similar secondary GLM subgroup analyses of the nonresponders who accepted additional therapy, there was a trend indicating an interaction effect ($F = 2.93$; $p = 0.063$; observed power = 0.54). The AD nonresponders who accepted additional PDT had improved significantly less between weeks 8 and 24 (mean T0: 20.17; mean T8: 20.08; mean T16: 17.00; mean T24: 15.75) than the PDT nonresponders who accepted additional AD (mean T0: 21.53; mean T8: 22.35; mean T16: 15.71; mean T24: 10.94).

Discussion

Stepped care strategies seem clinically logical, but about 40% of the patients declined the offer of additional therapy in this study, despite the limited effect of monotreatment. The acceptance rate was similar in both conditions. Given the widespread support for and implementation of stepped care and sequential treatment strategies [13–15], this was a rather unexpected finding. In the STAR*D trial, psychotherapy (cognitive therapy) as a sequential step also proved difficult to implement after unsuccessful AD treatment [27, 60]. However, some clear obstacles reported in the STAR*D trial, such as travelling to a different department and no payment by insurance companies, were absent from our sample.

As in STAR*D, the decision to proceed with combined therapy in our study was based on the independent assessment of HAM-D scores. However, the HAM-D does not differentiate between core depression symptoms – such as mood, anhedonia or suicidal thoughts – and accessory symptoms like lack of appetite or sleeping problems [61–64]. Nor does it measure patients' own evaluations of the relative importance of symptoms, which may be a more decisive factor in the decision to accept a new therapy option than symptom change only.

A total of 38% of all patients included at the outset of the study dropped out, mainly in the first 8 weeks. Pharmacotherapy in depression has often been associated with high drop-out rates varying from 30 to 68% [65, 66], especially during the first month of treatment.

Reported psychotherapy drop-out rates in depression vary from 10 to 50% [67–70]. Settings similar to ours also found drop-out rates of around 40% [9, 71]. Consequently, we do not assume that drop-out is caused by the psychodynamic feature of the psychotherapy.

A study by Warden et al. [72] indicated that the initial intent of the patient with respect to continuing treatment is more relevant for drop-out than perceived side effects or a lack of efficacy during treatment. Discussing intent with patients at risk of drop-out before the start of therapy could therefore enhance adherence, alongside telephone support [66] and motivational interviewing [73].

The main issue addressed by this study was the efficacy of sequential strategies. Overall, the group receiving PDT from the outset is better off at the end of the acute phase of treatment. The AD strategy produced better results in the first 8 weeks (significantly lower HAM-D scores and more responders). However, from week 16 onwards, the pattern of results was reversed and, at week 24,

the PDT group overtook the original AD group in most of the assessments, including quality of life scores.

A partial explanation of the fact that the PDT sequential strategy produces better results emerges from the findings from the secondary analyses: the PDT patients who refused pharmacotherapy also remitted without ADs and they were better off in relative terms than the AD patients who refused additional psychotherapy. Another – additional – explanation is that pharmacotherapy responders lost their gain of the first 8 weeks, as opposed to the PDT responders who enhanced their gain (a finding that emerged from the secondary analyses). Secondary analyses indicated that, with the CGI-I, clinicians tended to overestimate the actual result of pharmacotherapy compared to patient reports. It may be advisable to use more specific instruments than the CGI, such as a short form of the HAM-D [74], which can be easily administered during pharmacotherapy consultations.

Additional psychotherapy or pharmacotherapy after unsuccessful monotreatment produced significantly better results than no additional therapy. This result is comparable with those of Frank et al. [16] and the STAR*D study [27]. Nevertheless, because of the quasi-experimental design from week 8 onwards in this study, we do not know the precise reasons for the better results of the additional therapy approach. It is possible that the preference for addition affected factors such as hope and/or positive expectations, with a positive impact on outcome [75].

There are several factors that may have affected the validity of this study and that should be addressed. The study population was restricted to outpatients with mild to moderate depressive episodes. We did not take into account the influence of personality factors or attitude towards treatment options and these may be associated with both the acceptability and efficacy of treatment strategies [76]. Furthermore, we did not take into account subtypes of depression [77–79] and the decision to change therapy was based solely on insufficient improvement based on the HAM-D. However, treatment resistance may also be related to an inadequate approach to different subtypes of depression. As Bech [80] pointed out, primary depression and secondary depression associated with anxiety and pursuant to childhood trauma or in response to separation stress may require specific treatment options.

Finally, patients were only offered two options for additional therapy (PDT or AD). They did not have the option of other AD treatments or different forms of psychotherapy, combined therapy from the outset, psychosocial support or long-term psychotherapy, or augmentation of dose [81].

On the other hand, there were also enough strengths. At week 8, patients were not randomized at that point but offered a choice. Despite the complexity of this quasi-experimental design, we see it as a strength because it involves a choice that approximates the real world and enhances the external validity of the study. The fact that the data were from multiple sources (independent observers, patients and therapists) is also a strength, as was our implementation of the sequential strategy.

This study shows that patients receiving psychotherapy from the outset were, compared to those receiving pharmacotherapy, better off by week 24, when treatment ended. In both groups, proceeding to combined therapy after initial nonresponse appeared to be a beneficial strategy after early nonresponse to monotreatment.

There was a trend in which the patients who initially responded to pharmacotherapy failed to improve any further and patients who did respond and who receive psychotherapy continued to improve throughout the treatment.

Finally, in order to investigate the usefulness of sequential and stepped care strategies, complex and, from a scientific point of view, suboptimal designs have to be used.

Our study indicates that such studies are possible and could generate new data about the effectiveness of sequential strategies that are frequently used in day-to-day clinical practice.

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