The efficacy of short-term individual interpersonal psychotherapy in augmentation with pharmacotherapy in major depressive disorder

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Background
The high prevalence rates and persistently increasing burden of depression indicate that there are still many unmet needs in the management of depression. Interpersonal psychotherapy (IPT) is one of the main evidence-based psychotherapeutic interventions for depression.
Aim
To evaluate the efficacy of short-term individual IPT in combination with pharmacotherapy, compared with pharmacotherapy alone, in the treatment of depression and assess its role in improving social functioning.
Setting and design
This study was conducted in Mansoura University hospitals and was an interventional randomized controlled trial.
Patients and methods
A total of 40 patients were recruited and randomized into either the interventional group or the control group. The interventional group received IPT in combination with selective serotonin reuptake inhibitor. IPT was in the form of once weekly session for 12 weeks. Patients in the control group received treatment with an selective serotonin reuptake inhibitor with appointments once every 2 weeks. Patients from both groups were assessed by the Montgomery–Asberg Depression Rating Scale and the Social Adjustment Scale Self-Report at the beginning and after 12 weeks.
Statistical analysis
IBM SPSS Statistics version 20.0 was used for statistical analysis.
Results
There were highly statistically significant improvements in depressive symptoms and in social functioning between the baseline assessments and after 12 weeks on the used scales in both groups. There was a trend for better improvement in the interventional group (IPT+pharmacotherapy) in depressive symptoms and in overall and specific domains of social functioning when compared with the control group. The interventional group showed statistically significant better improvements in social functioning when compared with the control group.
Conclusions
Combined IPT and pharmacotherapy shows clear benefits over pharmacotherapy alone, in both alleviating depressive symptoms and improvement of social functioning.

Keywords:
combined psychotherapy and pharmacotherapy, depression, interpersonal psychotherapy

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Background

Depression is ranked the second leading cause of disability globally in all ages and sexes (Ferrari *et al.*, 2013; Gutiérrez-Rojas *et al.*, 2020). The high prevalence rates and persistently increasing burden of depression indicate that there are still many unmet needs in the management of depression (World Health Organization, 2015; Wittchen *et al.*, 2001; Tolin, 2010).

Successful treatment of depression is influenced by many factors beyond the properties of a particular medication. These include the unique characteristics of each patient, the safety–tolerability–effectiveness profile of the drug, and the interaction between patient and health care professionals (Butcher *et al.*, 2008). Although newer antidepressants represent significant improvements in safety and tolerability, the advances in therapeutic benefit are not

substantial. Shortcomings of current antidepressants include the delayed achievement of benefit, the percentage of patients not reaching response or remission, the continuity of adverse effects, and ~25% recurrence risk even if continued to be taken during maintenance (Kennedy *et al.*, 2006; Parker and Fletcher, 2007; Solomon *et al.*, 2008). Moreover, some patients do not respond to medications, or refuse to take them, or in many areas of the world just cannot afford them. For all of these patients, psychotherapies may have a utility (National Institute for Clinical Excellence NICE, 2004; American Psychiatric Association, 2010).

In practice, guidelines recommend both pharmacological and psychological interventions for depressive disorders (Ellis, 2004; National Institute for Clinical Excellence NICE, 2004).

The effectiveness of psychotherapy is documented by decades of scientific research (Wampold, 2010; Chorpita *et al.*, 2011; Cuijpers *et al.*, 2016). Thousands of quantitative and qualitative studies have shown that ~75–80% of patients who receive psychotherapy show benefit (Halverson, 2020; Pampallona *et al.*, 2004; Lambert, 2010).

Cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT) have been proven to be the best psychotherapy candidates to be used in combination with pharmacotherapy in the treatment of major depressive disorder (MDD) (Sudak, 2011; Cuijpers *et al.*, 2016). Both CBT and IPT are diagnosis-targeted, time-limited treatments that enable patients to re-claim control of their mood and functioning (Stuart and Robertson, 2012; Markowitz *et al.*, 2014; Pu *et al.*, 2017).

IPT is based on the link between depression and interpersonal life events. Within IPT, therapy focuses on the interpersonal relations as a way to bring out change, either through improving the interpersonal relationships or changing patients' expectations about them (Stuart and Robertson, 2012). IPT was developed for various types of clinical trials. For acute treatment trials, the length has ranged from 12 to 16 weeks; for continuation trials, weekly for 8 months; and for maintenance trials continued for three years (Cuijpers *et al.*, 2016). Weissman and other colleagues have proven the efficacy of IPT in the treatment of depression repeatedly in many clinical trials, and this success has led to its modification for use in other mood and non-mood disorders (Cuijpers *et al.*, 2016). Some trials have demonstrated the efficacy of IPT in treatment of depression in medically ill patients, peripartum women, depressed adolescents, geriatric depressed patients, and for recurrent or treatment-resistant depression (Pu *et al.*, 2017). Success with mood disorders has also led to the exploration of IPT as a treatment for other conditions. There have been promising developments of IPT as a treatment for social phobia, post-traumatic stress disorder, and eating disorders. IPT has also shown preliminary benefits for anxiety disorders (Markowitz *et al.*, 2014).

Patients and methods

The aim of this study was to evaluate the efficacy of short-term individual IPT in combination with pharmacotherapy, compared with pharmacotherapy alone, in the treatment of MDD, and assess its role in alleviating depressive symptoms and improving social functioning in a sample of Egyptian adult patients.

The design of this study is an interventional randomized controlled trial, with two parallel arms. This study was approved by the Mansoura Research Ethical Committee and was performed according to the ethical standards of the Helsinki Declaration. All included participants signed an informed consent form after explaining to them the details of the research goals, ensuring the confidentiality of the obtained data, and acknowledging their voluntary participation.

The study took place in the Mansoura University hospital psychiatry outpatient clinic, Dakahlia mental health hospital outpatient clinic, and some referred patients from private clinics in Mansoura city, Egypt. The study extended for 18 months from April 2014 to October 2015.

A total of 40 patients were recruited from the previously mentioned sites. Inclusion criteria were meeting the 'DSM-5' diagnostic criteria of MDD, age from 18 to 60 years old, Egyptian nationality, and giving informed consent. Exclusion criteria were presence of other comorbid psychiatric disorders, presence of comorbid substance-use disorder, presence of a comorbid chronic or severe medical illness, history of a previous 'manic or mixed or hypomanic episode,' history of receiving any kind of psychotherapy in the last year, and history of receiving psychotropic or antidepressant medication in the last 3 months.

A total number of 64 patients underwent screening for eligibility, and of those patients, 13 patients did not

meet the inclusion criteria and 11 patients refused to participate. The 40 patients who met inclusion criteria and gave informed consent were randomized to either the interventional group (*n*=20) or the control group (*n*=20). Randomization was on the basis of alternate allocation.

In the interventional group (*n*=20), only two patients were withdrawn from the study; one of them due to noncompliance with regular study appointments beyond the minimal acceptable limit, and the other one owing to noncompliance with study medications. In the control group (*n*=20), three patients were withdrawn from the study, all of them due to noncompliance with study medications. All five withdrawn patients were excluded from the statistical analysis of results.

The patients in the interventional group received individual IPT in combination with an selective serotonin reuptake inhibitor (SSRI) antidepressant (Escitalopram). IPT was in the form of once weekly session for 12 consecutive weeks (12 sessions). The minimum number of sessions accepted to fulfill the definition of sufficient therapy was ten sessions. Patients in the control group received 'treatment as usual' in combination with escitalopram. 'Treatment as usual' appointments in the control group were arranged to be once every 2 weeks for 12 weeks (six appointments). Patients in the interventional group also received treatment as usual, besides IPT. Treatment as usual included clinical assessment, checking for adverse effects, and unstructured psycho-education.

Patients with mild or moderate depression were administered escitalopram at a dosage of ten milligrams daily, whereas patients with severe depression were administered 10 mg daily during the first week, and 20 mg daily thereafter. This scheme was used for patients in both the interventional and control groups. Pharmacotherapy adherence and adverse effects were assessed using patient self-report. Patients in both groups were assessed by the Montgomery–Asberg Depression Rating Scale (MADRS) and the Social Adjustment Scale Self-Report (SAS-SR) twice during the study period: the first assessment at baseline before starting IPT or escitalopram, and the second assessment at the end of 12 weeks.

Efficacy was determined by intragroup differences and intergroup differences at two assessment points: at baseline and after 12 weeks. The primary domains assessed were depressive symptoms as measured by the clinician-rated MADRS and social functioning as measured by the SAS-SR.

The outcome measures are first MADRS (Montgomery and Asberg, 1979), which is used to assess the severity of depression among depressive patients. It is a 10-item diagnostic questionnaire. Every item has a score of 0–6, with the overall score ranging from 0 to 60. Higher MADRS score indicates more severe depression (McDowell, 2006; Williams and Kobak, 2008). It includes questions on the following symptoms: sadness (apparent), sadness (reported), inner tension, decreased sleep, reduced appetite, lassitude, concentration difficulties, inability to feel, pessimistic thought, and suicidal thoughts (Davidson *et al*., 1986).

Herrmann *et al*. (1998) proposed the following cutoff scores from 0 to 8=remission/symptoms absent, nine to 17=mild depression, 18–34=moderate depression, and more than or equal to 34=severe depression. The cutoff scores used in this study were those proposed by Herrmann *et al*. (1998) as those are most commonly used in clinical trials (Müller-Thomsen *et al*., 2005; McDowell, 2006).

The principal outcome measure in this study was the difference between the MADRS scores at baseline and those after 12 weeks. A 50% or more reduction in MADRS score at the endpoint from baseline score was used as an indicator of response (Frank, 1991), and an endpoint MADRS score of ten or less was used as an indicator of remission (Hawley *et al*., 2002). A 50% or more reduction in MADRS score with and endpoint score of more than ten is classified as a 'response without remission.' A reduction in MADRS score at the endpoint of less than 50% is an indicator of nonresponse.

The second is the SAS-SR (Weissman and Bothwell, 1976; Weissman, 1999; Weissman *et al*., 2001), which was designed as an outcome measure to evaluate drug treatment and psychotherapy for depressed patients. It is a 54-item paper-and-pencil self-report scale of social adjustment derived directly from the SAS interview, with wording of the questions changed to suit the self-report format. The self-report version has the advantage of being free from interviewer bias (Weissman and Bothwell, 1976). The scale includes a total of 54 questions, of which respondents answer 42 questions, which is because the method provides alternative questions on work relations for employed people, housewives, and students. It takes 20–30 min to

complete. The questions were designed to measure expressive and instrumental performance over the past 2 weeks in six role areas: work, social and leisure activities, relationships with extended family, role as a marital partner, role as a parent, and role as a member within the family unit, including perceptions about economic functioning (Gurland *et al.*, 1972). Questions in each role area cover four expressive and instrumental categories. Each question is rated on a five-point scale, with higher scores indicating more impairment. The SAS-SR generates seven mean scores: one for each of the six role areas, plus a score for the overall mean. The scores of items within each role area are summed and a mean for each role area is obtained, and an overall adjustment score is obtained by summing the scores of all items and dividing it by the total number of items answered.

An Arabic version of the SAS-SR was used after a process of translation and back-translation. The Arabic version was approved and verified through the department of foreign languages in the Faculty of Education in Mansoura University.

IPT is a time-limited diagnosis-based treatment originally used for patients with MDD, but later adapted for other disorders as well (Frank *et al.*, 2007). IPT was described in a manual by Klerman *et al.* (1984) and was updated by Weissman *et al.* (2000, 2007). Five different phases exist in the IPT approach: assessment phase, initial phase, middle phase, termination phase, and maintenance phase. In the assessment phase, a standard clinical interview is completed to determine the suitability of IPT for the patient. The therapist then proceeds through the initial phase of IPT with the goal of socializing the patient to IPT and creating the IPT focus. Then an interpersonal inventory and an interpersonal formulation are developed, and a contract is made with patient for a certain number of sessions (Stuart and Robertson, 2012). During the middle phase, the therapist and the patient address relevant problem areas using key IPT techniques (ideally one but can be more). In the termination phase, the therapist reviews progress in the problem areas with the patient and together plan for future problems. Maintenance sessions can continue to prevent relapse or to work through any unsolved problems, but after the negotiation of a new contract (Stuart and Robertson, 2012).

This study included the acute treatment phase only. IPT was administered weekly for 12 weeks, with the session length between 40 and 50 min. Of 18 patients who completed IPT, 15 received the 12 sessions throughout 12 weeks as planned. However, three patients missed two sessions and needed two more weeks to account for the missed sessions and complete the 12 sessions.

Regarding MDD treatment in adults, systematic reviews and meta-analyses continue to support the idea that all the SSRIs have similar effectiveness, efficacy, and effects on quality of life. However, some clinically important differences among specific drugs do exist with respect to the onset of action and side effects (Halverson, 2020). Escitalopram was chosen in this study to represent pharmacological treatment of MDD with SSRIs. Escitalopram, the active isomer of citalopram, is a highly SSRI and has shown better efficacy in the treatment of severe depression, both in effect size and time of onset of action (Azorin *et al.*, 2004). It is well tolerated in MDD; adverse events are generally mild to moderate and transient, and no additional events are observed with long-term use. In a recent multiple-treatment meta-analysis, escitalopram and sertraline have shown the best profile of acceptability (Cipriani *et al.*, 2009).

All of the data were collected, formulated, and statistically analyzed using 'IBM SPSS Statistics' version 20.0. (IBM Corp., Released 2011, Armonk, New York, USA).

Results

The sociodemographic characteristics of patients in both interventional and control groups were comparable regarding age, sex, marital status, current living condition, residence, education, and employment, with no statistically significant difference between the two groups (Table 1).

Table 2 presents the baseline clinical characteristics of patients in both interventional and SSRI groups. There was no statistically significant difference between the two groups. As shown, the two groups were matched and comparable regarding the number of previous episodes, the age of the first episode, the duration of the current episode, and the severity rating of the current depressive episode on the MADRS.

Regarding the number of previous episodes, 47.5% of patients had no previous depressive episodes, 27.5% had a single previous episode, 17.5% with two previous episodes, and 7.5% with three previous episodes. Regarding the age of the first depressive episode, 45% of patients had their first depressive episode in

Table 1 Sociodemographics of patients in both interventional (interpersonal psychotherapy+selective serotonin reuptake inhibitor) and control (selective serotonin reuptake inhibitor) groups

	IPT group (*N*=20) [*n* (%)]	Control group (*N*=20) [*n* (%)]	Significance	Total (*N*=40) [*n* (%)]
Age group (years)				
18–30	7 (35.0)	5 (25.0)		12 (30.0)
31–40	6 (30.0)	7 (35.0)	χ^2=0.52	13 (32.5)
41–50	3 (15.0)	3 (15.0)	*P*=0.91	6 (15.0)
51–60	4 (20.0)	5 (25.0)		9 (22.5)
Sex				
Male	8 (40.0)	6 (30.0)	χ^2=0.44	14 (35.0)
Female	12 (60.0)	14 (70.0)	*P*=0.51	26 (65.0)
Marital status				
Single	8 (40.0)	6 (30.0)	χ^2=0.48	14 (35.0)
Married	9 (45.0)	10 (50.0)	*P*=0.78	19 (47.5)
Divorced	3 (15.0)	4 (20.0)		7 (17.5)
Current living condition				
Alone	4 (20.0)	5 (25.0)	FET	9 (22.5)
With family	16 (80.0)	15 (75.0)	*P*=1	31 (77.5)
Residence				
Urban	14 (70.0)	9 (45.0)	χ^2=2.56	23 (57.5)
Rural	6 (30.0)	11 (55.0)	*P*=0.11	17 (42.5)
Education				
Preparatory	2 (10.0)	4 (20.0)	χ^2=1.15	6 (15.0)
Secondary	5 (25.0)	6 (30.0)	*P*=0.56	11 (27.5)
University	13 (65.0)	10 (50.0)		23 (57.5)
Employment				
Employed	4 (20.0)	9 (45.0)		13 (32.5)
Housewife	6 (30.0)	4 (20.0)	χ^2=3.14	10 (25.0)
Student	7 (35.0)	4 (20.0)	*P*=0.37	11 (27.5)
Unemployed	3 (15.0)	3 (15.0)		6 (15.0)

χ^2, χ^2 test; FET, Fisher exact test; IPT, interpersonal psychotherapy.
**P* value significant less than or equal to 0.05.

Table 2 Clinical characteristics of patients in both interventional (interpersonal psychotherapy+selective serotonin reuptake inhibitor) and control (selective serotonin reuptake inhibitor) groups

	IPT group (*N*=20) [*n* (%)]	Control group (*N*=20) [*n* (%)]	Significance	Total (*N*=40) [*n* (%)]
Number of previous depressive episodes				
Mean±SD	1±1.03	0.7±0.92	*Z*=0.988	
Median (minimum–maximum)	1 (0–3)	0 (0–3)	*P*=0.32	
Zero	8 (40.0)	11 (55.0)		19 (47.5)
One	6 (30.0)	5 (25.0)	χ^2=1.04	11 (27.5)
Two	4 (20.0)	3 (15.0)	*P*=0.79	7 (17.5)
Three	2 (10.0)	1 (5.0)		3 (7.5)
Age of 1st depressive episode				
18–30	11 (55.0)	7 (35.0)		18 (45.0)
31–40	4 (20.0)	6 (30.0)	χ^2=2.78	10 (25.0)
41–50	2 (10.0)	5 (25.0)	*P*=0.43	7 (17.5)
51–60	3 (15.0)	2 (10.0)		5 (12.5)
Duration of current depressive episode (years)				
<1	15 (75.0)	15 (75.0)	χ^2=0.48	30 (75.0)
1–2	3 (15.0)	4 (20.0)	*P*=0.79	7 (17.5)
>2	2 (10.0)	1 (5.0)		3 (7.5)
Severity of current depressive episode on the MADRS				
Mild	4 (20.0)	5 (25.0)	χ^2=0.17	7 (20.0)
Moderate	9 (45.0)	8 (40.0)	*P*=0.92	15 (42.9)
Severe	7 (35.0)	7 (35.0)		13 (37.1)

χ^2, χ^2 test; IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale; *Z*, Mann–Whitney test.
**P* value significant less than or equal to 0.05.

the 18–30-year age group, 25% in the 31–40-years age group, 17.5% in the 41–50-year age group, and 12.5% in the 51–60-year age group. Considering the duration of the current depressive episode, the sample included 75% of patients with a duration of less than 1 year, 17.5% with a duration between 1 and 2 years, and 7.5% with a duration of more than 2 years.

Regarding the severity rating of the current depressive episode on the MADRS, based upon previously defined cutoff scores, the sample included 20% of patients with mild depression, 42.9% with moderate depression, and 37.1% with severe depression. There was no statistically significant difference between the two groups. The interventional (IPT) group included 20% of patients with mild depression, 45% with moderate depression, and 35% with severe depression. The controls group included 25% of patients with mild depression, 40% with moderate depression, and 35% with severe depression.

Table 3 shows the intragroup differences between measurements at baseline and after 12 weeks, expressed in mean MADRS scores. As shown, both groups reported significant improvement in depressive symptoms, and intragroup differences between baseline and week 12 assessments are highly statistically significant in both groups.

In addition, SAS-SR scores, in both groups, showed significant improvement in overall social functioning, and intragroup differences between baseline and week 12 assessments were highly statistically significant in both groups.

Table 4 presents the intergroup differences between measurements at baseline and after 12 weeks, expressed in mean MADRS and SAS-SR scores. At baseline, there were no significant differences in depressive symptoms on the MADRS and also in the level of overall social functioning on the SAS-SR between both groups, denoting successful randomization. Regarding the assessment after 12 weeks, there were no statistically significant intergroup differences detected on the MADRS (P=0.309). However, patients in the IPT group compared with those in the control group have shown notable greater decreases in depressive symptoms. On the contrary, the intergroup differences in the mean SAS-SR scores after 12 weeks showed that patients in the IPT group, compared with patients in the control group, reported significantly greater improvement in overall social functioning, resulting in a highly statistically significant intergroup difference (P<0.001).

Table 5 presents the outcome, in terms of response/nonresponse, and remission/nonremission in both

Table 3 Intragroup comparison of both interventional and control groups between baseline and after 12 weeks

	Baseline Mean±SD	After 12th week Mean±SD	Significance
IPT group (N=18)			
MADRS	31.39±8.2	10.94±5.14	t=10.72 P<0.001**
SAS-SR	3.35±0.61	2.04±0.36	t=13.58 P<0.001**
Control group (N=17)			
MADRS	29.35±8.91	12.88±5.96	t=11.67 P<0.001**
SAS-SR	3.47±0.63	2.73±0.52	t=9.19 P<0.001**

IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale; SAS-SR, Social Adjustment Scale Self-Report; t, paired t test.
*P value significant less than or equal to 0.05.
**P value highly significant less than or equal to 0.01.

Table 4 Intergroup comparison at baseline and after 12 weeks between interventional and control groups

	IPT group (N=18) Mean±SD	Control group (N=17) Mean±SD	Significance
MADRS			
Baseline	31.39±8.2	29.35±8.91	t=0.71 P=0.486
After 12th week	10.94±5.14	12.88±5.96	t=1.03 P=0.309
SAS-SR			
Baseline	3.35±0.61	3.47±0.63	t=0.589 P=0.56
After 12th week	2.04±0.36	2.73±0.52	t=4.54 P<0.001**

χ^2, χ^2 test IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale; SAS-SR, Social Adjustment Scale Self-Report; t, independent t test.
*P value significant less than or equal to 0.05.
**P value highly significant less than or equal to 0.01.

Table 5 Intergroup comparison of response and remission rates on the Montgomery–Asberg Depression Rating Scale after 12 weeks

	IPT group (*N*=18) [*n* (%)]	Control group (*N*=17) [*n* (%)]	Significance	Total (*N*=35) [*n* (%)]
Nonresponse	3 (16.7)	6 (35.3)	χ^2=1.59	9 (25.71)
Response	15 (83.3)	11 (64.7)	*P*=0.21	26 (74.29)
Nonremission	5 (27.78)	9 (52.94)	χ^2=2.31	14 (40.0)
Remission	13 (72.22)	8 (47.06)	*P*=0.13	21 (60.0)

χ^2, χ^2 test; IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale.
Nonresponse=reduction of baseline MADRS score of less than 50% at endpoint.
Response=reduction of baseline MADRS score of 50% or more at endpoint.
Nonremission=endpoint MADRS score of more than 10.
Remission=endpoint MADRS score of 10 or less.
**P* value significant less than or equal to 0.05.

Table 6 Mean Montgomery–Asberg Depression Rating Scale scores at baseline and after 12 weeks according to baseline depression severity

Severity	IPT group (*N*=18) Baseline MADRS score	One way ANOVA test	Control group (*N*=17) Baseline MADRS score	One way ANOVA test
Mild	17.67±1.53[ab]	*P*<0.001**	17±1.2[ab]	*P*<0.001**
Moderate	29.75±2.82[ac]		28.14±2.8 [ac]	
Severe	39.14±3.44[bc]		39±2.8 [bc]	
	12th week MADRS score		12th week MADRS score	
Mild	8±1	*P*=0.533	7.25±0.5[a]	*P*=0.014*
Moderate	11±5.6		12.14±4.34	
Severe	12.14±5.67		17.5±0.25[a]	

IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale.
**P* value significant less than or equal to 0.05.
***P* value highly significant less than or equal to 0.01.

Table 7 Intergroup comparison of Social Adjustment Scale Self-Report role areas mean scores at baseline and after 12 weeks

SAS-SR role areas	Time of measurement	IPT group (*N*=18) Mean±SD	Control group (*N*=17) Mean±SD	Significance
Work	At baseline	3.48±0.72	3.4±0.74	*t*=0.28 *P*=0.78
	After 12 weeks	2.08±0.69	2.52±0.56	*t*=1.91 *P*=0.07
Leisure	At baseline	3.64±0.58	3.83±0.72	*t*=0.865 *P*=0.39
	After 12 weeks	2.05±0.57	2.97±0.6	*t*=4.68 *P*<0.001**
Extended family	At baseline	3.29±0.74	3.51±0.77	*t*=0.86 *P*=0.39
	After 12 weeks	2.001±0.49	2.85±0.56	*t*=4.73 *P*<0.001**
Marital	At baseline	2.86±0.57	3±0.53	*t*=0.501 *P*=0.625
	After 12 weeks	1.69±0.34	2.42±0.56	*t*=3.007 *P*=0.009**
Parental	At baseline	3.25±0.72	3.81±0.81	*t*=1.087 *P*=0.291
	After 12 weeks	2.25±0.49	2.97±0.82	*t*=2.32 *P*=0.034*
Family unit	At baseline	3.29±0.71	3.41±0.79	*t*=0.476 *P*=0.638
	After 12 weeks	2.21±0.81	2.71±0.71	*t*=1.92 *P*=0.064

IPT, interpersonal psychotherapy; SAS-SR, Social Adjustment Scale Self-Report; *t*, independent *t* test.
**P* value significant less than or equal to 0.05.
***P* value highly significant less than or equal to 0.01.

groups. Thus, for both response and remission parameters, there was a remarkable greater difference in favor of the IPT group, but still statistical significance could not be detected.

Table 6 presents the mean MADRS scores, at baseline and after 12 weeks, according to baseline depression severity, in the IPT group and control group, respectively. As shown, there was a highly statistically significant difference, with respect to depression severity, at baseline in both groups, but after 12 weeks, a statistically significant difference was in the control group only.

Table 7 presents the intergroup differences between measurements at baseline and after 12 weeks in the six role areas of social functioning. At baseline, there were no significant differences in the level of social

Table 8 Correlations between Montgomery–Asberg Depression Rating Scale and Social Adjustment Scale Self-Report at baseline and after 12 weeks in the interventional group

	IPT group (*N*=18) MADRS	
	At baseline	After 12 weeks
SAS-SR		
At baseline	*r*=0.747 *P*=0.001**	*r*=0.29 *P*=0.28
After 12 weeks	*r*=0.424 *P*=0.102	*r*=0.63 *P*=0.01**

IPT, interpersonal psychotherapy; MADRS, Montgomery–Asberg Depression Rating Scale; *r*, Spearman correlation coefficient; SAS-SR, Social Adjustment Scale Self-Report.
**P* value significant less than or equal to 0.05.
***P* value highly significant less than or equal to 0.0.

functioning in any of the six role areas, between both groups, denoting successful randomization. After 12 weeks, patients in the IPT group, compared with patients in the control group, reported significantly greater improvement in four role areas of social functioning. As shown, intergroup difference in the remaining two role areas were also very close to statistical significance.

Table 8 presents the correlations in the IPT group between the MADRS scores and the SAS-SR scores, at baseline and after 12 weeks. There was a highly statistically significant strong positive correlation between the MADRS scores at baseline and the SAS-SR scores at baseline. In addition, there is a highly statistically significant moderate positive correlation between the MADRS scores after 12 weeks and the SAS-SR scores after 12 weeks.

Discussion

In terms of mean MADRS scores, the highly statistically significant intragroup differences between baseline and week 12 assessments in both groups corroborate the widely held view that both pharmacotherapy and combined therapy are efficacious treatments of depression. Several systematic reviews have examined the effects of both psychotherapy and pharmacotherapy and have shown that both therapeutic interventions are effective in the treatment of depressive disorders (Cuijpers *et al.*, 2008; Cuijpers, 2016; Karyotaki *et al.*, 2016). Moreover, significant improvement in overall social functioning was recorded, supporting the widely held view that social functioning and depression are closely related; depression is usually associated with impairment in social functioning, and improvement in depression is associated with improvement in social functioning (Lambert and Ogles, 2004; Lambert, 2010).

Although the difference in assessments after 12 weeks between the two groups on the MADRS were nonstatistically significant, a remarkable difference was shown in favor of the combined therapy group, and the *P* values suggest that a larger sample size could be able to detect a statistically significant difference between the interventional and control groups. However, there was a significantly greater improvement in overall social functioning in patients in the combined therapy group, compared with patients in the pharmacotherapy group. These findings support the view that IPT combined with pharmacotherapy has a significant additional benefit over pharmacotherapy alone in the improvement of social functioning (Guidi *et al.*, 2011).

In other relevant research, a meta-analysis of IPT for depression by Cuijpers *et al.* (2011) included 10 studies comparing combination of IPT and pharmacotherapy with pharmacotherapy alone and found a difference in favor of combination treatment. Likewise, this difference was not statistically significant, perhaps reflecting the small number of studies and consequent low statistical power (Cuijpers *et al.*, 2011).

In terms of response and nonresponse, 83.3% in the combined therapy group compared with 64.7% in the pharmacotherapy group met the MADRS response criteria. This is a remarkably high difference in response rates between both groups, in favor of the combined therapy group. Response rates in the pharmacotherapy group (64.7%) were very similar to those reported in a meta-analysis on efficacy of SSRIs of 65.8% (Kennedy *et al.*, 2006). Regarding remission and nonremission, 72.22% in the combined therapy group compared with 47.06% in the pharmacotherapy group met the MADRS remission criteria. This is also a remarkably high difference in remission rates between both groups, in favor of the combined therapy group.

Even though there was a remarkably high difference in favor of the IPT group in both response and remission rates, it is most likely that a statistically significant difference could not be detected because of the restricted sample size, and as the *P* values are very close to significance, it is most probable that a larger sample size could be able to detect a statistically significant difference.

A highly statistically significant difference was found in the intergroup comparison in the severely depressed patient group, in favor of combination therapy. Moreover, comparisons of response and remission rates according to severity have also shown better improvement in the severely depressed patients with combined therapy but not with pharmacotherapy. The

intergroup comparison in response and remission rates in patients with severe depression revealed remarkable yet nonstatistically significant differences in favor of the combination therapy group. These findings are similar to those reported by other researchers (Cuijpers *et al*., 2015).

Several studies suggest that CBT and IPT may have specific effects when competently implemented but only for patients with more severe depression. Among studies that considered balance with respect to severity, specific effects were found nearly only among patients with more severe depression, and that applies with respect to both psychotherapy and medications (Thase and Conolly, 2020; Driessen *et al*., 2010; Fournier *et al*., 2010). Some call this the 'dirty little secret' of pharmaceutical industry, which has long selectively screened out patients with less severe depression (in order to up the odds of finding drug-placebo differences required to win FDA approval) and then turns around and markets those same medications to people who it knows fully well are likely to respond for purely psychological reasons (Kirsch, 2010).

Intragroup differences between baseline and week 12 assessments on the SAS-SR were highly statistically significant in all the six role areas in both groups. Patients in the IPT group compared with patients in the control group reported significantly greater improvement in four role areas of social functioning (parental, marital, leisure, and extended family role areas). These findings support the view that IPT combined with pharmacotherapy has a significant additional benefit over pharmacotherapy alone in the improvement of social functioning, in both overall functioning and specific role areas (Weissman *et al*., 2014; Bright *et al*., 2020). These findings maintain the widely held view that social functioning and depression are closely related; depression is usually associated with impairment in social functioning, and improvement in depression is associated with improvement in social functioning (Kraus *et al*., 2019).

In relevant research, a recent meta-analysis by Cuijpers (2016) found clear evidence that combined treatment with psychotherapy and pharmacotherapy may be the best treatment available for adult depression and that it is significantly more effective than treatment with pharmacotherapy alone (Cuijpers, 2016). However, until now, it has not been well established whether the effects of pharmacotherapy and those of psychotherapy are complementary to each other, or independent from each other, or whether combined treatments lead to higher effects than the sum of the two treatments alone (Friedman *et al*., 2004; Otto *et al*., 2005).

According to Stahl (2012), there has always been a competition between psychopharmacology and psychotherapy, but as psychopharmacology became the main treatment in psychiatry, this approach is heavily criticized as limited with nonrobust outcomes and affected by the drugs industry. He has shown that the recent advances in neurobiology are illuminating that learning and environmental experiences, such as psychotherapy, change brain circuit, as do drugs. In another way, Stahl considered that psychotherapy, as therapeutic agents, is capable of acting epigenetically in a way similar or complementary to drugs. This view has the potential of making the entire effect greater than the sum of the parts, or 1+1=3, the delightful 'bad math' of therapeutic synergy (Stahl, 2012).

The main limitation of this study is its sample size and should be viewed as a preliminary study. Another limitation was the use of a single psychotherapist. Because this is a small study, the provision of IPT by a single therapist decreases generalizability and allows attribution of the results to the therapist rather than the therapy. The question whether specific IPT techniques, or therapeutic factors common to different psychotherapies, contribute more to outcome in psychotherapy is still debatable.

Conclusions

Both the combined therapy (IPT+SSRI) and pharmacotherapy (SSRI) groups had highly statistically significant and clinically relevant improvements in depressive symptoms and in social functioning, between the baseline assessments and assessments after 12 weeks.

The combined therapy (IPT+SSRI) group showed statistically significantly better improvement in social functioning when compared with the pharmacotherapy (SSRI) group.

The combined therapy (IPT+SSRI) group has shown remarkable but nonstatistically significantly better improvement in depressive symptoms when compared with the pharmacotherapy (SSRI) group.

Patients in the combined therapy (IPT+SSRI) group had remarkably higher response and remission rates than patients in the pharmacotherapy (SSRI) group (83.3% response and 72.22% remission compared with 64.7% response and 47.06% remission, respectively).

Severely depressed patients have shown remarkably better improvement with combined therapy (IPT +SSRI) but not with pharmacotherapy (SSRI) alone.

Larger trials are needed with enough statistical power to detect modest effects when comparing combined therapy with pharmacotherapy in the treatment of depression.

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Conflicts of interest
There are no conflicts of interest.

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