Predictors and moderators of response to internet-delivered Interpersonal Psychotherapy and Cognitive Behaviour Therapy for depression

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ABSTRACT

Background: By identifying which predictors and moderators lead to beneficial outcomes, accurate selection of the best initial treatment will have significant benefits for depressed individuals.

Method: An automated, fully self-guided randomized controlled internet-delivered noninferiority trial was conducted comparing two new interventions (Interpersonal Psychotherapy [IPT; n=620] and Cognitive Behavioral Therapy [CBT; n=610]) to an active control intervention (MoodGYM; n=613) over a period of 4 weeks to spontaneous visitors of an internet-delivered therapy website (e-couch). A range of putative predictors and moderators (socio-demographic characteristics [age, gender, marital status, education level], clinical characteristics [depression/anxiety symptoms, disability, quality of life, medication use], skills [mastery and dysfunctional attitudes] and treatment preference) were assessed using internet-delivered self-report measures at baseline and immediately following treatment and at six months follow-up. Analyses were conducted using Mixed Model Repeated Measures (MMRM).

Results: Female gender, lower mastery and lower dysfunctional attitudes predicted better outcome at post-test and/or follow-up regardless of intervention. No overall differential effects for condition on depression as a function of outcome were found. However, based on time-specific estimates, a significant interaction effect of age was found. For younger people, internet-delivered IPT may be the preferred treatment choice, whereas older participants derive more benefits from internet-delivered CBT programs.

Limitations: Although the sample of participants was large, power to detect moderator effects was still lacking.

Conclusions: Different e-mental health programs may be more beneficial for specific age

groups. The findings raise important possibilities for increasing depression treatment

effectiveness and improving clinical practice guidelines for depression treatment of different age

groups.

1. INTRODUCTION

The effectiveness of Cognitive Behavioral Therapy (CBT) and Interpersonal Psychotherapy (IPT) have been well established (Cuijpers et al., 2011a, b). Both have been found to be similarly effective in reducing depressive symptoms (Cuijpers et al., 2011a). However, less is known about who will benefit from therapy, and who will not. Even when two treatments are found to be equally effective in reducing depressive symptoms, individual characteristics may influence treatment outcome. Predictors (pre-treatment variables which predict depressive outcome in all treatment groups; Kraemer et al., 2002) and moderators (pre-treatment variables identifying which individuals are more likely to benefit from a particular treatment; Kazdin, 2007) are important to identify for several reasons. By identifying which characteristics of an individual predict the outcome of a specific treatment, a better match of treatment to the individual characteristics is achievable (Cuijpers et al., 2012; Simon and Perlis, 2010). Hence, this might contribute considerably to improvement of available treatments (Hamburg and Collins, 2010; Katsanis et al., 2008; Topol and Lauer, 2003). Knowledge about predictors and moderators of treatment outcome improves clinical decision about treatment (Andersson et al., 2008; MacKinnon, 2012), which has flow on effects to lower costs, reduce time in therapy, and enhance implementation and dissemination of depression treatment in the community. Furthermore, moderator analyses can detect whether a lack of intervention effect may be attributable to the intervention having opposite effects for different subgroups (Kraemer et al., 2006; MacKinnon, 2012).

1.1 Predictors of face-to-face depression interventions

Previous research has indicated that age (Fournier et al., 2009), pre-treatment level of dysfunctional attitudes (Blatt et al., 2010; Bulmash et al., 2009; Driessen and Hollon, 2010; Jacobs et al., 2009; Ravitz et al., 2011; Simons et al., 1984; Thase et al., 1991), and pre-treatment depression severity (Driessen and Hollon, 2010) may be predictors in response to traditional IPT and/or CBT. However, none of these studies has been designed to examine these predictors, and are based on post-hoc analyses.

1.2 Moderators of face-to-face depression interventions

The limited evidence on moderators suggests that being married moderated treatment outcome favorably in Cognitive Therapy (CT) compared to IPT whereas non-married people performed better in IPT compared to CT (Barber and Muenz, 1996). Barber and Muenz (1996) also found CBT superior to IPT for patients with avoidant personality traits and IPT superior to CBT for patients with obsessive personality traits. Furthermore, results from a clinical trial of IPT vs. CBT for depression suggested that subjects with more severe depression performed better with CBT (Luty et al., 2007) and those with avoidant and schizoid personality disorder symptoms predicted poorer response to IPT but not to CBT (Joyce et al., 2007).

1.3 Predictors of internet-interventions for depression

Immediately accessible and less costly, internet-delivered interventions may offer a valuable alternative to face-to-face therapy. Previous studies and meta-analyses have demonstrated unguided Internet-delivered self-help interventions to be effective for common mental disorders, with a pooled effect size of 0.28, but dropout rates are high (Cuijpers et al., 2011c). Internet-delivered CBT and IPT self-help interventions for depression are shown to be effective (Cuijpers

et al., 2010; Donker et al., 2013) and guided self-help has shown to be as effective as face-to-face therapy (Cuijpers et al., 2010), but it may be that other processes are responsible for therapeutic change compared to face-to-face treatment. In the few internet-delivered CBT depression mechanism studies, the results have been inconclusive. For example, low pre-treatment illness severity and short-term improvement on clinical variables predicted better depression outcome (De Graaf et al., 2010), and Andersson et al., (2005) found that the number of previous depression episodes predicted poorer treatment response at six months follow-up. However, several studies have reported that higher pre-treatment depression scores predicted better internet-delivered CBT outcome (Button et al., 2011; Spek et al., 2008; Warmerdam et al., in press), whereas in another study, pre-treatment depression score was not associated with internet-delivered CBT outcome (Proudfoot et al., 2003). Spek et al. (2008) showed that female gender predicted better outcome for Internet-delivered CBT for depression. Marital status (being divorced, widowed or separated) was also associated with greater internet-delivered CBT treatment response (Button et al., 2011). Education level, age or depression history did not influence treatment outcome for internet-delivered CBT for depression (Button et al., 2011).

1.4 Moderators of internet-interventions for depression

Moderator research of internet-delivered treatment for depression is sparse. One study found that those scoring higher on the altruism personality characteristic performed better in group CBT compared to internet-delivered CBT (Spek et al., 2008). Another study (Warmerdam et al., in press) found no moderators in their internet-delivered CBT study.

Given the paucity in mechanism research for internet-delivered interventions for depression, and IPT in particular, the aim of this study was to identify predictors and moderators for participant's

treatment outcome of internet-delivered IPT and CBT. We hypothesized that baseline characteristics (e.g., gender, age, educational level, marital status, baseline depression level, skills, and previous depression) would moderate or predict treatment effects.

2. METHODS

2.1. Participants and procedure

The current study is a secondary analysis of a previously outcome study (Donker et al., 2013), in which the details of the participants and procedure have already been described. In short, this automated, three-arm, fully self-guided internet-delivered noninferiority trial compared two new interventions (IPT-e-couch and CBT e-couch) to an active comparator intervention (MoodGYM) for depressed individuals. The trial was designed within a noninferiority framework. Noninferiority trials are used when there is clear evidence of efficacy for an existing standard treatment, such that it is ethically unacceptable to employ a placebo or inactive control group (Pocock, 2003) and when a new treatment is hypothesized to have comparable, but not necessarily superior, effectiveness to the established intervention (Mascha and Sessler, 2011). There was no specific promotion for the trial. Individuals were spontaneous visitors from around the world to an automated internet-delivered program (e-couch). The e-couch website is well known and promoted in communities around the world as a free and accessible source of personal self-help. Participants aged 18 years or older who gave informed consent and were not currently receiving treatment for depression by a mental health specialist were included in the study. Individuals with suicide intention or those who scored above 27 (95th percentile or higher) on the CES-D at baseline, were immediately provided with an information page containing

advice about obtaining appropriate professional help, including emergency help. They could, however, continue to participate in the study. Study participants were randomly assigned to MoodGYM, CBT or IPT. We minimized exclusion criteria to increase generalizability of results. Excluded were health professionals treating people with depression/anxiety, researchers reviewing depression/anxiety sites, or students studying anxiety or depression as part of a college or university course. Individuals who were excluded from the study were directed to the public version of the e-couch program. Ethical approval for the study was provided by the Human Research Ethics Committee of the Australian National University (ANU).

2.2 Interventions

All programs were offered over 4 weeks. Users were required to complete the modules in order. Participants were able to revisit previous pages of the modules and scores of previous assessments, but were not able to repeat the assessments. Exercises were not compulsory. Each week an automated email was sent to advise participants of the availability of their new module. Participants were always offered the option to pause and restart at their chosen time.

2.2.1 Internet-delivered Cognitive Behavioural Therapy (CBT)

CBT is based on the cognitive theory that negative automatic thoughts, maladaptive information processing, and avoidance behavior play a key role in the development and maintenance of depression (Beck et al., 1979). The Internet-delivered CBT intervention comprised one 'component' of the depression stream of e-couch (www.ecouch.anu.edu.au) and is based on the principles of CBT (Beck et al., 1979). In addition to an explanation of the rationale of CBT, the program consists of three major modules, namely, identifying negative thoughts, tackling

negative thoughts and undertaking behavioural activation (based on activity scheduling developed by Lewinsohn (1975). The program contains 18 exercises and assessments in total, which are saved in a personal workbook.

2.2.2 Internet-delivered Interpersonal Psychotherapy (IPT)

IPT originates from interpersonal theory (Klerman et al., 1987). It links stressful life events and insufficient social support to the development and maintenance of depressive symptoms (Weissman et al., 2007). IPT's most important message is that it is possible to change how you feel by changing the way you interact with people. The internet-delivered form of IPT comprised one 'component' of the depression stream of e-couch, which consists of four modules (grief, role disputes, role transition and interpersonal deficits) and a personal workbook (containing 13 exercises and assessments). The Grief module contains strategies and examples how to cope with grief. The Role Disputes module provides information about the importance of relationships, contains interactive exercises to map user`s relationships, their expectations and disputes, and provides strategies to resolve disputes. The Role Changes module provides psychoeducation about role changes and how to manage them, supported by interactive exercises. The interpersonal deficits module handles strategies to improve relationships. The IPT program was based on the IPT clinician manual of Weissman et al., (2007), with each of the four IPT areas constructed to reflect the areas and topics relevant to each area. Interactive exercises reflected the topics and questions described in the Interpersonal Inventory. Participants did not choose IPT areas, but could decide the order in which they were completed.

2.2.3 Internet-delivered CBT (MoodGYM)

The internet-delivered CBT package comprised a 4-module version of MoodGYM (www.moodgym.anu.edu.au) delivered over 4 weeks. The details of the program are described elsewhere (Christensen et al., 2002; 2006). In this trial, a set of four of the CBT modules, a personal workbook (containing 22 exercises and assessments) and a feedback evaluation form were used. The modules cover the identification of and behavioral modification methods to overcome dysfunctional thinking, assertiveness and self-esteem training respectively. Behavioural methods to overcome dysfunctional thinking included identification of negative thoughts and common thinking errors and evaluating them through examples of fictional characters, interactive personal exercises and online workbook. In addition, the Pleasant Events Schedule was used to increase social and physical activity. Each module undertakes 20-40 minutes (Christensen et al., 2006). The relaxation module was removed from the program for this study to equate the time length of the programs. Previous research has demonstrated that this component is not needed for efficacy (Christensen et al., 2006).

2.3 Measures

All questionnaires comprised standard internet-delivered self-report measures. Measures were taken at baseline (pre-test), immediately after the intervention (post-test) and 6 months after the intervention (follow-up). Measures of participant characteristics were collected at baseline, while symptom measures were administered at all time points.

2.3.1 Potential predictors and moderators of outcome

2.3.1.1 Demographic and baseline outcome measure

Socio-demographic characteristics (age, gender, marital status, education level) were examined

for predictor effects (whether the characteristic predicts depressive outcome in all groups) and moderator effects (whether the characteristic identifies individuals who are more likely to benefit from a particular treatment).

2.3.1.2 Illness severity levels

Depressive symptoms: The 20-item Center for Epidemiological Studies Depression scale (CES-D; Radloff, 1977) was used to assess baseline depressive symptoms (item score: 0–3; total score range: 0–60). The Internet CES-D is reliable and valid with a cut-off score of 22 (Donker et al., 2010). The Cronbach's α in this study was 0.90.

Previous history for depression: Previous history of depression ("Do you have a previous history of depression?") was measured using a dichotomous variable (yes, no).

Disability: Severity of baseline disability was measured with the Days Out of Role questions adapted from the US National Comorbidity Survey, which included 1 question about 30-day role impairments resulting from problems with depression. Good concordance has been documentedwith payroll records of employed people (Kessler et al., 2003).

Anxiety symptoms: Severity of baseline worrying was measured with the 7-item GAD-7 (Spitzer et al., 2006). Item scores range between 0–3 while total scores range 0–21. The internet-delivered version of the GAD-7 has demonstrated good internal reliability and convergent validity (Donker et al., 2011). Cronbach's α in the present study was 0.87.

Quality of life: Baseline quality of life was measured with the 8-item EUROHIS-QOL. This scale has good internal consistency and a satisfactory convergent and discriminant validity (Schmidt et al., 2005). Cronbach's α in the present study was 0.78.

Medication use: Medication use was measured using a dichotomous variable (yes, no) indicating whether participants were using prescribed or over-the-counter medication for mental health problems at baseline.

2.3.1.3 Skills

Mastery: The baseline 7-item Mastery Scale (Pearlin and Schooler, 1978) was used to assess perceived control. Scale scores range from 1 to 5, with total scores ranging 7-35. A high score (internal mastery) indicates that someone has the feeling of being in control of situations. The questionnaire has good psychometric properties (Pearlin and Schooler, 1978). Cronbach's α in the present study was 0.76.

Dysfunctional attitudes: Two 9-item short forms (SF) of the Dysfunctional Attitudes Scale (DAS; Weismann and Beck, 1978) were used to assess cognitive vulnerability in depression at baseline. The DAS-SF, measuring perfectionism and the need for approval (DAS-SF1 and DAS-SF2; Beevers et al., 2007), were highly correlated with the original 40-item DAS, exhibited change similar to that of the DAS over the course of treatment, were moderately correlated with related self-report assessments, predicted concurrent depression severity, and predicted change in depression from before to after treatment (Beevers et al., 2007). The reliability of the DAS-SF in the present study was Cronbach's α=0.91.

2.3.1.4 Treatment preference

Preference for randomisation condition ("Do you have a preference to be in one of the programs?", "no preference", "yes, program 1, 2, 3") at baseline was included in the analyses (no preference, preference: match /no match).

2.3.2 Outcome: depressive symptoms

The CES-D depression score was used as the dependent variable.

2.4 Statistical analyses

Baselines characteristics were tabulated for each of the treatment groups, and differences across the three groups were assessed using one-way ANOVA for continuous variables and chi-square tests for categorical variables. To examine possible differences between the programs, between-group and within-group effect sizes were calculated according to Cohen`s *d* (standardised mean difference; Cohen, 1988). To examine the putative predictors and moderators of treatment response, Mixed Model Repeated Measures (MMRM) analysis was used. Restricted maximum likelihood estimation was used with an unstructured variance-covariance structure accommodation with participant effects. MMRM gives unbiased estimates of ITT effects under the assumption that data from participants who withdrew were missing at random (MAR). Time was treated as a categorical variable, as we were interested in the differences between groups on each occasion of measurement. The CES-D score was treated as the dependent variable. Independent variables were the putative baseline predictors/moderators, treatment group and the treatment $\times$ time interaction term. To test whether baseline variables moderated treatment outcome, separate MMRM models were constructed including the effects of the moderator, time, condition, time $\times$ condition, moderator $\times$ condition, moderator $\times$ time and the 3-way interaction of moderator $\times$ condition $\times$ time. The potential moderators were entered individually due to the large number of interaction terms and to mitigate potential multicollinearity issues. Omnibus Type 3 tests were used to test for significance of the effect of the moderator on treatment effects across all time points. All continuous baseline variables were treated as continuous variables to

maintain power. All statistical analyses were conducted using SPSS version 20.0 (IBM

Corporation, Somers, NY, USA).

3. RESULTS

3.1. Baseline characteristics, treatment adherence and drop-out

Details of the participant flow and drop-out is described elsewhere (Donker et al., 2013). Of the

total sample (N=1,843), the majority (59%) were under 40 years of age, and female, (n=1,334;

72.4%). Participants were mainly Australian residents and most completed tertiary education

(n=1,606; 87.2%). The mean CES-D baseline score was 36.0 (SD: 11.5). CES-D scores of 27 or

more indicative of major depression (Ensel, 1986; Zich et al. 1990). There were no significant

differences between the groups at baseline with respect to clinical or demographic

characteristics, except for age group. Significantly more participants over 60 years of age

participated in in the MoodGYM program (see Table 1).

In total, 30% of participants completed post-test and 28% completed follow-up. Those

who dropped out of treatment had significantly higher scores on the CES-D, χ^2 (1,1843) = 4.28,

p=0.039), but differences were small (Mean Difference: 1.26). Drop-out rates were significantly

higher for participants assigned to MoodGYM (n=451; 35%) compared to IPT (n=414; 32%) or

CBT (n=429; 33%), χ^2 (2, 1843) = 6.817, p=0.03. Non-responders (those who dropped out of

treatment) were more likely to be female (n=914; 71%), χ^2 (1, 1843) = 6.64, p= 0.01, and under

50 years of age (n=1090; 84%), χ^2 (1, 1843) =21.59, p <0.001. No significant differences were

found for medication use (p=0.73), treatment preference (p=0.14) or marital status (p =0.60).

3.2 Treatment effectiveness

Completer analyses showed a significant reduction in depressive symptoms at post-test and follow-up for both CBT and IPT, and were noninferior to MoodGYM. Within-group effect sizes were medium to large for all groups. There were no differences in clinical significant change between the programs. Reliable change was shown at post-test and follow-up for all programs, with consistently higher rates for CBT. Participants allocated to IPT showed significantly lower treatment satisfaction compared to CBT and MoodGYM. There was a dropout rate of 1294/1843 (70%) at post-test, highest for MoodGYM. The intention-to-treat analyses yielded medium within-group effect sizes (d=0.59 to d=0.67 at post-test and d=0.66 to d=0.80 at follow-up). Between-group effect sizes were small (post-test: IPT vs. MoodGYM: d=0.09 (95% CI:-.02-0.21); CBT vs. MoodGYM: d=0.01 (95% CI: -.010-0.12); follow-up: IPT vs. MoodGYM: d=0.09 (95% CI: -.02-0.21), CBT vs. MoodGYM: d= 0.03 [95% CI: -0.08-0.14]). See Donker et al. (2013) for a full description on the programs` effectiveness.

3.3 Predictors of response to intervention

Results of multivariate MMRM analysis of predictors of depression outcome at post-test and follow-up are shown in Table 2. Participants who had more days out of role due to depression, whose treatment matched their preference, who had higher scores on the GAD-7 or who had lower Euro-QOL or mastery scores at baseline, had higher CES-D scores overall, as reflected in the significant main effects in Table 2. More importantly, the significant interactions with time in Table 2 indicated that females, participants with lower mastery scores and participants with lower dysfunctional attitudes scores, had greater reductions in depressive symptoms at post-test and/or follow-up relative to baseline. Specifically, the effects of female gender ($t_{439.0} = 2.39$, $p = 0.017$) and lower dysfunctional attitudes ($t_{439.0} = -2.57$, $p = 0.011$) were only significant at post-

test, while the effect of lower mastery was significant at post-test ($t_{439.0} = -7.24$, $p < 0.001$) and follow-up ($t_{279.0} = -3.85$, $p < 0.001$).

3.4 Moderators of response to intervention

MMRM Analyses on moderators of depressive symptoms after internet-delivered IPT, CBT and MoodGYM are presented in Table 3. None of the 3-way interactions was significant overall, suggesting there were no significant moderation effects. However, estimates at specific time points were also examined for each model, and the 3-way age $\times$ condition $\times$ time interaction had significant effects for specific conditions at either the post-test or follow-up assessment. Specifically, at follow-up, older participants in the MoodGYM condition had larger improvements in depression scores than those in the IPT condition, whereas younger participants (16-24) in the IPT condition had larger improvements in depression scores than those in the MoodGYM condition (See Figure 1; For ease of interpretation, the three older age groups has been combined). This difference was significant for the 25-39 ($t_{378.4} = 3.47$, $p = 0.001$), 40-59 ($t_{379.7} = 2.11$, $p = 0.035$) and ≥ 60 age groups ($t_{383.7} = 2.66$, $p = 0.008$) relative to the 16-24 age group for the comparison of IPT and MoodGYM from baseline to follow-up. The difference between 16-24 and 25-39 in the comparison between IPT and MoodGYM was also significant from baseline to post-test ($t_{583.6} = 1.98$, $p = 0.048$). This trend was not significant for the other age groups at post-test. The models were re-estimated with IPT as the reference category. Based on this version of the model, there was a lesser difference between IPT and CBT, although there was a significant difference between 16-24 and 25-39 (but not other age groups) from baseline to follow-up ($t_{378.1} = 2.79$, $p = 0.006$). The direction of the CBT-IPT difference was the same as the MoodGYM-IPT difference: older participants in the CBT condition had larger improvements in depression scores than those in the IPT condition, whereas younger participants (16-24) in the

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IPT condition had larger improvements in depression scores than those in the CBT condition. Although the Type III omnibus tests of condition × time and age × time were also not significant, IPT participants had significantly greater decreases in depression scores than MoodGYM participants at follow-up ($t_{378.3} = -2.50$, $p = 0.013$) and 25-39 year-olds had greater improvements than 16-24 year-olds at follow-up ($t_{377.2} = -2.36$, $p = 0.019$).

3.5 Sensitivity analysis of moderators

Models were re-estimated with the MoodGYM and CBT groups combined to test whether the effects were associated with the content of the intervention. In this analysis, the Type III omnibus test was significant ($F_{6, 472.0} = 2.86$, $p = 0.010$), indicating treatment response over time differed according to age group. Differences were observed between IPT and CBT-based conditions from baseline to post-test for the 25-39 ($t_{589.1} = 2.17$, $p = 0.031$) and 40-59 groups ($t_{593.2} = 2.25$, $p = 0.025$) compared to the 16-24 group. From baseline to follow-up, there were differences in intervention responses between all three age groups and the 16-24 group (25-39: $t_{384.0} = 3.74$, $p < 0.001$; 40-59: $t_{385.2} = 2.38$, $p = 0.018$; ≥60: $t_{389.5} = 2.69$, $p = 0.008$). These differences were in the same direction as the primary model: older participants in the CBT-based conditions had larger improvements in depression scores compared to the IPT condition, whereas younger participants (16-24) in the IPT condition had larger improvements in depression scores than those in the CBT-based conditions. No additional significant three-way interactions emerged in these secondary analyses.

3.5 Post-hoc power calculations

Conservative power estimates to find a three-way interaction effect between age group, time and condition were calculated by estimating power to find a difference between the two smallest age

groups within a single condition at the follow-up assessment. At follow-up, the two smallest age groups were within the MoodGYM condition, with sample sizes of 13 and 18. There was 26% power to detect a moderate effect between these two groups, assuming an independent groups *t*-test with two tails, alpha = .05. Of course, many other subgroups had larger samples, particularly for independent variables with fewer categories, and this estimate did not take into account that considerably greater power was available through the MMRM procedure than for a *t*-test, particularly for finding a difference at post-test. For example, at post-test there was 79% power to find a difference between males and females in the MoodGYM condition based on identical assumptions but with 41 males and 121 females. Nevertheless, the conservative estimate suggests there was limited power to find moderation effects based on three-way interactions in the present sample, largely due to high attrition.

4. DISCUSSION

4.1 Main findings

The aim of this study was to identify predictors and moderators in three Internet-delivered CBT and IPT programs for depressive symptoms. As far as we know, no studies to date have examined predictors and moderators of change with respect to internet-delivered IPT for depression.

4.2 Predictors

Female gender, lower mastery scores and lower dysfunctional attitudes predicted greater reductions in depressive symptoms at post-test and/or follow-up compared to baseline. Our finding that females generally improve more in CBT or IPT compared to men has been found

previously (e.g., Frank et al., 2008; Spek et al., 2008) and might be explained in that women perhaps are generally more willing to express their thoughts and feelings than men. In addition, men might improve more using other types of therapies (e.g, Behavioral Activation; Lewinsohn, 1975). Consistent with previous research (Sotsky et al., 1991), better depression outcome was associated with lower dysfunctional attitudes at baseline. One explanation might be that people with higher levels of dysfunctional attitudes are less able to benefit from treatment due to higher levels of bias in information-uptake processes. Interestingly, and inconsistent with previous studies (Button et al., 2011; Spek et al., 2008; Warmerdam et al., in press), baseline depression severity was not significantly associated with treatment outcome in the present study. This may be attributed to relatively high baseline depression scores of the majority of our study-sample. This may be attributed to depression scores being in the high range for the majority of our sample, unlike in other community-based samples. Hence, there may have been insufficient variability in baseline depression scores to detect a significant association between low and high severity. No overall differential effects for condition on depression outcome were found. *4.3 Moderators*

Based on the time-specific estimates in the moderator analysis, a significant interaction effect of age was found. Specifically, at follow-up, older participants in the CBT-based conditions had larger improvements in depression scores than those in the IPT condition, whereas younger participants (16-24 years) in the IPT condition had larger improvements in depression scores than those in the CBT-based conditions. Additional analyses to test if therapy content explained a difference yielded similar results. This is interesting, because MoodGYM was originally developed for young people. These results indicate that younger people might benefit more from IPT-content-based psychotherapy, whereas older participants may benefit most from CBT-based

programs. Trials of face-to-face IPT-based interventions for prevention of depressive disorders have found very strong effects of IPT on the incidence of depressive disorders in adolescents (Young et al., 2006; Merry et al., 2012; Munoz et al., 2010), but results are inconclusive. One study found that adolescents administered face-to-face CBT improved to a greater extent than adolescents receiving face-to-face IPT (Rosello et al., 2008). However, the authors of this study reported that the fidelity of the IPT program was low and thus the reliability of the study findings is unclear. One explanation for the finding in our study that younger individuals benefitted more from IPT than CBT, might be that some of the foci in IPT, such as interpersonal conflicts and role transitions, might be especially relevant for adolescents, who are very likely to experience more stressors during their transition from childhood to adulthood and may be more prone to interpersonal conflicts due to, amongst others, hormonal changes and stressors. However, further study is required to determine whether such effects can be explained by higher levels of interpersonal conflict among young people. The finding that younger participants did worse with MoodGYM echoes a previous MoodGYM study (Calear et al., 2009) in a younger age group (12-17 years), in which the effects on depressive symptoms were less strong, particularly amongst females. Perhaps the cognitive and reading demands of the MoodGYM program might be too high for a younger audience, in spite of that the program was originally designed for a young audience. Again, interpersonal issues may be a larger determinant of depression symptoms in younger people than older. Unfortunately, there is no information about relationship status, only marital status. While it is true that a smaller proportion of the younger age group was married/living with partner than among the older age groups, we have no data on whether unmarried individuals were in a relationship. Nevertheless, it may be inferred that relationship issues are more salient for those who were not married. In the current study, no other variables

differentially predicted outcome for the different interventions. This could imply that the mechanisms of action are similar despite the difference in content of the programs or that differential effects were present but not detectable due to insufficient statistical power.

4.4 Implications

Accurate selection of the optimal initial treatment could have tremendous benefits for people living with depression, with treatment tailored to maximize the factors that contribute to better outcomes. Information about moderators may provide unique new and valuable information to guide future restructuring of diagnostic classification and treatment decision-making, to inform the selection of inclusion and exclusion criteria, and the choice of stratification variables to maximize power in randomized controlled trials (Kramer and Wilson, 2002). In our study we found a moderator effect of age. If replicated, these findings have the potential to increase evidence-based treatment allocation of participants, suggesting that younger people may receive greater benefit from IPT whereas those over 25 are more likely to experience reductions in depression symptoms through CBT. The findings raise important possibilities for increasing depression treatment effectiveness and improving clinical practice guidelines for depression treatment of different age groups.

4.5 Limitations

This study has several limitations. First, although the sample of participants was large, power to detect moderator effects was still lacking. Large sample sizes needed for this type of analysis is difficult to attain for logistical and economic reasons. To overcome this problem, large databases from depression treatment studies could be combined to enable Individual Patient Data (IPD) meta-analyses to be undertaken. In IPD meta-analyses, primary patient data of all individual

studies (which are already collected) are combined and examined, overcoming the problem of insufficient power (Simon et al., 2010). Nevertheless, this study is a critical first step in moderator research of internet-delivered IPT. Secondly, there was a high drop-out rate. Drop-out was high among all conditions, a finding that is common for Internet interventions. High drop-out rates are likely with minimal exclusion criteria, unguided interventions (Andersson et al., 2009; Newman et al., 2003), and little or no financial commitment (Eysenbach, 2005). Although MRMM was used to appropriately account for missing data, response bias cannot be ruled out. Third, in addition to research on predictors and moderators, improvement of depression treatment might be enhanced by investigating potential mediators. Unfortunately, we were unable to perform these analyses due to the research design (noninferiority design) and the absence of assessments at multiple time-points during the intervention period. Fourth, at commencement of the trial, participants were excluded if they received concurrent treatment. However, because of ethical reasons, participants could seek additional help if they presented high depression or suicide ideation scores during the period of the trial. it was unknown whether participants used other treatments during the study. This could mask real differences between groups if this use of additional treatments was more prevalent for one group compared with the others. However, given the large sample size and randomization procedure, we do not expect that this would influence results greatly. Fifth, the high rate of subjects with high education has commonly been found in previous studies examining internet-delivered interventions for mental health problems (e.g.; Warmerdam et al., 2008). However, it may hamper generalizability of findings to subjects with lower education levels. Sixth, subjects were asked whether they used current prescribed or over-the-counter medications. Since over-the-counter medications may not have any significant effect on mood, this item might be of limited value. Finally, there was no in-

or exclusion criteria related to depression to increase generalizability of results. Therefore, it is unknown what kind of people participated in this study. However, analyses indicated that the majority of the sample (n=1737, 94.3%) had a CES-D score above the clinical cut-off score of 22 (Donker et al., 2013). Furthermore, effectiveness of the three programs did not differ between non-clinical and clinical cases of depression (Donker et al., 2013). Therefore, it is unlikely that this may influence our results.

4.6 Future research

Further research is needed to examine moderators of internet-intervention compared to face-to-face interventions, and whether the usage of short text, more visuals, interactive videogames, and other delivery types (e.g., WII, apps) in internet-delivered mental health interventions are more beneficial to younger participants than older participants. In addition, investigation of secondary outcomes may better identify the processes by which the interventions may lead to reductions in depression. Furthermore, our results require replication and further investigation, particularly the finding that internet-delivered IPT is more beneficial for younger people than CBT interventions, and that conversely older participants gain more benefit from internet-delivered CBT-based interventions than IPT interventions. In particular, further study is required to determine whether such effects can be explained by higher levels of interpersonal conflict among young people. Finally, additional research into mediator and moderator effects is needed, which is likely to require IPD meta-analyses.

4.7 Conclusions

In sum, this study suggests that different e-mental health programs may be more beneficial for specific age groups. For younger people, internet-delivered IPT may be the preferred treatment choice, whereas older participants may derive more benefit from internet-delivered CBT programs.

CONFLICTS OF INTEREST

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Table 1

Table 1. *Pre-treatment characteristics: Means (standard deviations) and frequencies (percentages)*

	IPT N=620	CBT N=610	MoodGYM N=613	
Demographic variables				*p value*
Age group:				0.02
18-24	115 (18.5)	92 (15.1)	100 (16.3)	
25-39	253 (40.8)	272 (44.5)	257 (41.9)	
40-59	221 (35.6)	223 (36.6)	206 (33.6)	
>60	31 (5.1)	23 (3.8)	50 (8.2)	
Gender (female)	451 (72.7)	445 (73.0)	438 (71.5)	0.82
Education level:				0.31
None, or primary	6 (1.0)	4 (0.7)	11 (1.8)	
Secondary	79 (12.7)	67 (11.0)	70 (11.4)	
Tertiary	535 (86.3)	539 (88.3)	532 (86.8)	
Partner (yes)	303 (48.9)	310 (50.8)	301 (49.1)	0.81
Severity variables				
Depression (CES-D)	36.38 (11.86)	36.29 (11.04)	35.34 (11.61)	0.21
Anxiety (GAD-7)	11.62 (5.28) n=608	11.66 (5.19) n=601	11.53 (5.19) n=607	0.94
Quality of life (EUROHIS-QOL)	20.83 (5.79) n=600	20.82 (5.45) n=590	20.97(5.59) n=597	0.89
Disability (days due to depression)	15.47 (13.64) n=576	15.02 (13.99) n=575	13.67 (13.21) n=576	0.07
Medication use (yes)	246 (39.7)	255 (41.8)	253 (41.3)	
Previous history of depression (yes)	572	550	545	0.13
Skill variables				
Dysfunctional attitudes	47.65 (9.38) n=565	47.30 (8.98) n=559	47.04 (9.58) n=569	0.54
Mastery	16.67 (3.69) n=585	16.75 (3.49) n=578	16.79 (3.55) n=568	0.85
Other				
Treatment preference (match)	113	109	116	0.73

Abbreviations: CBT = Cognitive Behavior Therapy; IPT= Interpersonal Psychotherapy; CES-D: Center for Epidemiological Studies Depression scale; GAD-7: Generalized Anxiety Disorder-7

Table 2

Table 2. *Potential predictors of depressive symptoms after internet-delivered IPT, CBT and MoodGYM with multivariate MMRM analysis (ITT)*

Source	F	df	*p* value
Intercept	104.2	1, 406.8	<0.001
Time	1.3	2, 351.4	0.276
Condition	1.3	2, 390.7	0.268
History of depression	0.0	1, 393.4	0.953
Age group	0.2	3, 390.8	0.899
Gender	0.1	1, 383.3	0.726
Education	1.1	2, 421.5	0.327
Marital status	0.6	3, 363.1	0.611
Medication use	0.1	3, 474.5	0.956
Treatment preference	6.8	1, 377.6	**0.009**
GAD-7 score	35.6	1, 385.4	**<0.001**
DAS score	1.0	1, 405.2	0.319
Euro-QOL score	44.9	1, 379.6	**<0.001**
Days out of role‑ depression	21.4	1, 379.9	**<0.001**
Mastery score	89.0	1, 397.8	**<0.001**
Time interaction terms			
Condition	0.8	4, 352.6	0.523
History of depression	1.5	2, 354.0	0.235
Age group	0.8	6, 350.7	0.565
Gender	3.4	2, 341.9	**0.036**
Education	2.4	3, 382.8	0.067
Marital status	1.9	6, 321.1	0.085
Medication use	0.8	5, 357.7	0.582
Treatment preference	1.2	2, 334.7	0.310
GAD-7 score	2.1	2, 344.4	0.129
DAS score	3.3	2, 366.5	**0.038**
Euro-QOL score	2.5	2, 337.2	0.080
Days out of role‑depression	1.4	2, 337.5	0.241
Mastery score	26.6	2, 358.9	**<0.001**

*Notes: **bold** values indicate p < 0.05; estimates are Type III omnibus tests from a multivariate mixed model repeated measures analyse. GAD: Generalized Anxiety Disorder; DAS: Dysfunctional Attitudes Scale; Euro-QOL: European health-related Quality of Life scale; IPT: Interpersonal Therapy; CBT:Cognitive Behavioral Therapy; MRMM: Mixed Model Repeated Measures*

Table 3

Table 3. *Three-way interactions of mediator × condition × time for potential moderators of depressive symptoms after internet-delivered IPT, CBT and MoodGYM: Mixed Models Repeated Measures analyses (ITT)*

	F	df	*p* value
Age	1.496	12, 471.2	0.122
Gender	0.395	4, 465.1	0.812
Education	1.444	4, 505.4	0.218
Marital status	0.878	8, 452.7	0.535
Medication use	0.730	10, 469.7	0.697
GAD-7 score	0.419	4, 480.0	0.795
DAS score	0.564	4, 483.8	0.689
Euro-QOL score	0.601	4, 494.2	0.662
Days out of role - depression	0.691	4, 457.3	0.598
Mastery score	0.960	4, 456.9	0.429
Treatment preference	0.483	4, 461.2	0.748
History of depression	0.994	4, 493.3	0.410

Notes: estimates are Type III omnibus tests for three-way interactions with time and condition, taken from separate mixed models repeated measures analyses; GAD: Generalized Anxiety Disorder; DAS: Dysfunctional Attitudes Scale; Euro-QOL: European health-related Quality of Life scale

Figure 1

Figure 1: *Age as a moderator of depressive symptoms after internet-delivered IPT, CBT and MoodGYM with multivariate MMRM analysis (ITT)*
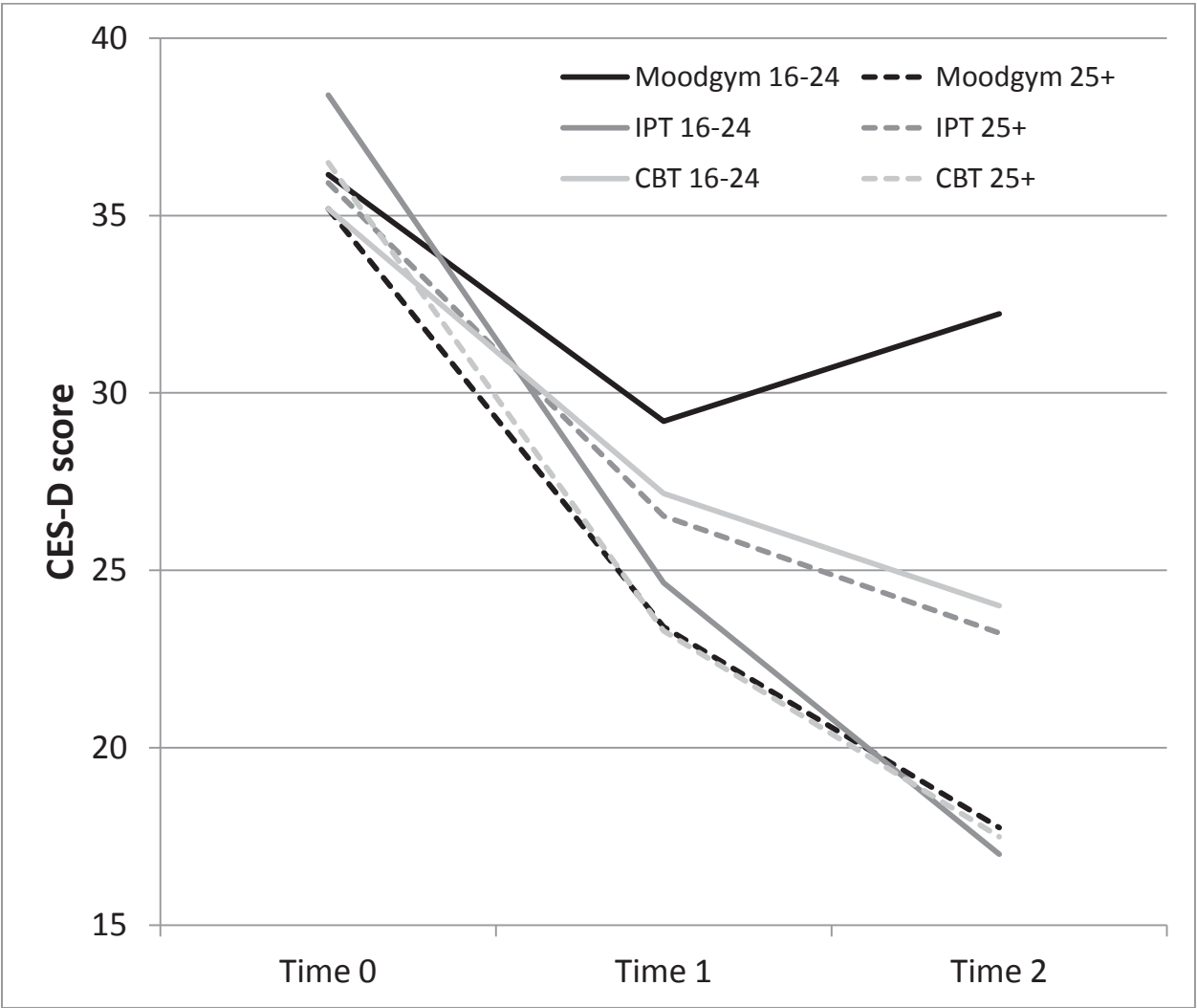
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CONTRIBUTORS

Authors TD, KG and HC designed the study and wrote the protocol. Author TD managed the literature searches and analyses. Authors TD and PB undertook the statistical analysis, and author TD wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

CONFLICTS OF INTEREST

The interventions investigated in the current study were developed at the Centre for Mental Health Research, The Australian National University. H.C. and K.G. are authors and developers of the MoodGYM and eCouch websites but derive no personal or financial benefit from their operation.

ROLE OF THE FUNDING SOURCE