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EDITORIAL

What we know, what we do not know, and where are we heading? Efficacy and acceptability of psychological interventions for depression

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In the past several decades, increasing evidence supports the efficacy of psychotherapies for depression. The vast majority of findings from meta-analyses, randomized clinical trials (RCTs) and naturalistic studies have demonstrated that well-established psychotherapies (behavioural activation, problem-solving therapy, psychodynamic therapy, cognitive-behavioural therapy, interpersonal therapy and emotion-focused therapy) are superior to no-treatment and control conditions, and are in most cases equally effective in treating depression. However, despite this abundant support for psychotherapies, studies have also consistently shown high drop-out rates, high percentages of non-respondent patients who experience treatment failures, and mixed findings regarding the enduring effects of psychotherapy. Thus, there is a need to develop more personalised treatment models tailored to patients' needs. A new integrative sequential stepwise approach to the treatment of depression is suggested.

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What do we know about the efficacy of psychotherapies for depression?

Depression is a pervasive mental condition which interferes with all domains of one's functioning and it is one of the most common problems leading people to seek treatment (e.g. Summers & Barber, 2010). Recent studies have shown that the approximated cumulative incidence of depression diagnosis from childhood to adulthood is between 32.54 and 51% (Rohde *et al*. 2012; Angst *et al*. 2015).

In the past several decades, over 400 randomised clinical trials have investigated the efficacy of psychotherapy for depression (Cuijpers, 2015). Despite the heated debate regarding the superiority of one treatment over others, there is fairly wide acceptance of the 'Dodo Bird Verdict' (Luborsky *et al*. 1975), at least in the case of depression, suggesting that all treatments are more or less equally effective (Cuijpers *et al*. 2008; Barth *et al*. 2013). Furthermore, research in the past two decades has taught us that psychotherapeutic treatments of depression are superior to wait-list and other control conditions (Barth *et al*. 2013; Lambert, 2013), and that psychotherapy combined with anti-depressant medication is more effective than medication alone (Barber *et al*. 2013; Köhler *et al*. 2013; Hollon *et al*. 2014; Fonagy, 2015; Leichsenring *et al*. 2015). There is also evidence suggesting that some types of psychotherapies are not only as effective as medication, but also have higher long-term enduring effects (Hollon & Ponniah, 2010; Cuijpers *et al*. 2013*b*). We begin by briefly reviewing some of the major findings that have arisen from the literature on treatments of depression, focusing only on the best-known and more widely researched.

Behavioural activation (BA)

BA is one of the most accepted and widely used behavioural treatments. Meta analyses found BA to be as effective as cognitive-behavioural therapy, and superior to control conditions (Cuijpers *et al*. 2007; Mazzucchelli *et al*. 2009) and to medication (Ekers *et al*. 2014). Dimidjian *et al*. (2006) also showed that BA was superior to cognitive therapy and as effective as medication.

Problem-solving therapy (PST)

PST is a cognitive-behavioural treatment which emerged from behaviour modification research (D'Zurilla & Goldfried, 1971; Nezu *et al*. 1989). PTS was found to

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be superior to medication and as effective as other alternative psychosocial therapies and medication (Bell & D`Zurilla, 2009). However, another meta-analysis showed that the effects of PST vary across studies, ranging from close to zero to very large effects (Cuijpers *et al*. 2007).

Short-term dynamic psychotherapy (STDP)

STDP emerged from the work of Malan (1976), Mann (1973), Sifneos (1979), Davanloo (1980) and Luborsky (1984). Randomized clinical trials (RCTs) and meta-analyses have shown that STDP is as effective as medication (Barber *et al*. 2012), more effective than control conditions, and as effective as alternative treatments at termination and follow-up assessments (Driessen *et al*. 2010, 2013, 2015*a*, *b*, Gibbons *et al*. 2012; Abbass *et al*. 2014; Fonagy, 2015; Leichsenring *et al*. 2015). Furthermore, combined treatment of STDP and medication was found to be more effective than medication alone (Barber *et al*. 2013; Fonagy, 2015; Leichsenring *et al*. 2015).

Long-term dynamic psychotherapy (LTDP)

There is evidence supporting the effectiveness of LTDP and psychoanalysis (de Maat *et al*. 2009), especially in long-term follow-ups (Knekt *et al*. 2008, 2011; Huber *et al*. 2013). There is also some indirect evidence that LTDP is superior to other psychotherapies in treating complex patients with chronic depression and previous treatment failures (Leichsenring & Rabung, 2008, 2010; Fonagy *et al*. in press). However, some of these conclusions have been challenged (e.g. Smit *et al*. 2012).

Cognitive-behavioral therapy (CBT)

CBT, pioneered by Beck *et al*. (1979), became the most widely studied treatment for depression. Robust evidence supports its superiority over control conditions (DeRubeis *et al*. 2005; Tolin, 2010; Cuijpers *et al*. 2013*a*; Marcus *et al*. 2014), and some studies found that combined treatment is superior to medication alone (Cuijpers *et al*. 2013*a*; Köhler *et al*. 2013; Hollon *et al*. 2014). When comparing CBT to alternative treatments, there are mixed findings (Hofmann *et al*. 2012). While some meta-analyses reported the superiority of CBT (e.g., Tolin, 2010; Marcus *et al*. 2014), they have been criticised (Leichsenring & Rabung, 2010; Baardseth *et al*. 2013), and others found that it is as effective as alternative treatments (e.g. Leichsenring, 2001; Cuijpers *et al*. 2008, 2013*a*; Beltman *et al*. 2010; Driessen *et al*. 2013, 2015*b*).

Interpersonal therapy (IPT)

Interpersonal psychotherapy (IPT) emerged from Sullivan's (1953) interpersonal theory and was later adapted for depression (Klerman *et al*. 1984). In a large RCT, Elkin *et al*. (1989) found that IPT is equally effective to medication and CBT, with some evidence for increased efficacy of IPT for severely depressed patients. There is also preliminary evidence suggesting the superiority of IPT over alternative psychotherapies (Cuijpers *et al*. 2008, 2011), specifically supportive counselling (Barth *et al*. 2013) and CBT (de Mello *et al*. 2005).

Emotion-focused therapy (EFT)

EFT emerged from the humanistic, experiential and client-centred therapeutic approaches (Greenberg & Watson, 2006). Experiential therapies were found slightly more effective than non-treatment and control conditions (ES = 0.12; Elliott *et al*. 2004); however, effects largely varied in magnitude and direction. Studies found that adding emotion-focused techniques to client-centred therapy increased the efficacy of treatment (Greenberg & Watson, 1998; Goldman *et al*. 2006), and that EFT was superior to client-centred therapy in long-term follow-ups (Ellison *et al*. 2009). Watson *et al*. (2003) found in an RCT that EFT equal to CBT but superior in reduction of interpersonal problems. Overall, while preliminary evidence supports the efficacy of EFT, there is still a need for future research comparing EFT to placebo, control and alternative psychotherapies.

Strengths and weaknesses of meta-analyses

In this paper, we base many of our arguments on data from meta-analyses. While meta-analyses are an important source of information, providing reviews and summaries of large numbers of studies, we are also aware of their limitations. Specifically, the quality of a meta-analysis derives in part from the quality and thoroughness of the studies included in it. Considering quality in determining the conclusion from a meta-analysis is not a simple proposition (Kocsis *et al*. 2010; Gerber *et al*. 2011; Thoma *et al*. 2012). One can include study quality as a moderator in one's meta-analysis, as some researchers have done; however, this is not common practice and may reflect the authors' biases. More specifically, if a meta-analysis is not all-inclusive, it may be biased in one direction and could suffer from the author's 'allegiance' (see Leichsenring & Rabung, 2010; Baardseth *et al*. 2013). Thus, taking those limitations into account, we surmise that meta-analyses provide a rich and valuable source

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of information, although the specifics require close scrutiny. One important question for the field is whether to prefer the results of a meta-analysis which includes several average quality studies to those of several high-quality trustworthy specific RCTs which suggests the superiority of treatment A over a control condition (Hollon, personal communication, 2015).

What we still do not know about treatment of depression: remission and drop-out rates, enduring effects and treatment-resistant forms of depression

Remission rates

The ultimate goal of all treatments of depression is remission. It is often thought that if a treatment was given in an appropriate dose and duration and it did not end with remission, it cannot be considered successful (John Rush *et al*. 2006; Hollon *et al*. 2014). However, in depression, it is possible for response and remission to occur without treatment with estimated high rates of spontaneous remission ranging from 23% within 3 months to 53% within 12 months (Whiteford *et al*. 2013). Therefore, efficacious treatments are expected to result in significantly higher remission rates and/or a much quicker recovery time.

Despite the well-established benefits of treating depression over no treatment, findings from RCTs and naturalistic studies show that remission rates are far from 100% across all treatment modalities. Specifically, one of the largest RCTs (STAR*D), which tested the efficacy of sequential treatment allocation of medication and cognitive therapy, reported an overall remission rate of 27.5–32.9% (Trivedi *et al*. 2006), with decreasing rates from 32.9% in step 1 to 14.7% in step 4 (John Rush *et al*. 2006). These findings clearly call for a need to improve our treatment modalities.

In fact, in face of the low remission rates, NIMH director Insel (2009, 2006), emphasised a pressing need to develop new approaches to diagnosing and treating depression. As a result, most NIMH funding resources have shifted towards researching new neurobiologically based approaches to mental illnesses using NIMH's new diagnostic system – the Research Domain Criteria (RDoC) (e.g. Cuthbert & Insel, 2013). In the context of treating depression, the NIMH has been moving towards the development of personalised interventions based on the specific needs and circumstances of each individual patient.

Drop-out rates

Premature discontinuation, also referred to as dropout, is a major concern as it impedes the effectiveness of treating depression (Cahill *et al*. 2003). While dropout rates vary, premature discontinuation is a problem shared by all psychotherapies. A recent meta-analysis found a mean rate of 17.5% dropout in therapies for depression, with a large variance across studies ranging between 0 and 50% (Cooper & Conklin, 2015). Another meta-analysis (Flückiger *et al*. 2014) found 29.2% drop-out rate in evidence-based treatments (EBT) for acute depression and anxiety disorders (compared with 32.7% rate in treatment-as-usual control conditions (TAU)). Meta-analyses comparing dropout rates in different psychotherapies have yielded mixed findings, from equal dropout rates across treatments (Cooper & Conklin, 2015), to significant differences between psychotherapies, with the highest rate in CBT and the lowest rate in PST (Cuijpers *et al*. 2008). Taken together, these findings demonstrate the strong need to develop new treatment models tailored to patients' needs.

Enduring effects of psychotherapy

While ample evidence supports the efficacy of psychotherapies for depression at the endpoint of treatment, much less is known about their enduring effects. Some researchers found that different psychotherapies are effective in preventing relapse/recurrence (Hollon *et al*. 2006; Hollon & Ponniah, 2010; Steinert *et al*. 2014; Biesheuvel-Leliefeld *et al*. 2015) and that their enduring effects are as effective as a continuous use of medications (Cuijpers *et al*. 2013*b*). In contrast, others have shown that the superiority of EBT for acute depression and anxiety disorders over TAU is minimal on 0–4-month follow-ups, and does not extend at 8–12-month follow-ups (Flückiger *et al*. 2014).

These mixed findings indicate the need to study the long-term effects of psychotherapy (Lambert, 2013). The lack of evidence may largely be due to the major limitations of follow-up research. First, in some countries, there is no detailed information about patients' treatment utilisation and researchers need to rely on self-reports, which are often biased. Second, patients' frequent reluctance to participate in follow-ups often results in a large amount of missing data.

Treatment resistant depression

Accumulating evidence has shown that depression is a pervasive and chronic disorder and that many patients do not benefit from standard treatments. Researchers have identified a 43% recurrence of episodes among depressed young adults and 5–19% of suicide attempts among depressed patients aged 5–30 (Rohde *et al*. 2012). These findings have led investigators to focus

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on 'treatment-resistant' forms of depression (Taylor *et al*. 2012). Studies attempting to identify patient characteristics, which are more highly correlated with – or predictive of – high dropout rates and/or poorer outcome, have resulted in mixed findings. Some researchers found comorbidity of personality disorders and social racial minority status to be predictive of higher dropout rates (Cooper & Conklin, 2015). Others reported that these characteristics did not moderate the superiority of EBT over TAU, but rather identified additional moderators such as comorbidity of substance abuse (Flückiger *et al*. 2014). These contrasting findings demonstrate the need to develop more effective ways to treat non-responders (Barrett *et al*. 2008).

Where are we heading?

A suggestion for an alternative stepwise sequential model of allocation of treatment for depression

This paper reviewed the significant progress in the development and research of EBT for depression in the past few decades. However, evidence of high dropout rates, large non-responsive populations and mixed findings regarding the enduring effects of psychotherapy suggest that there is still much to be learned about the treatment of depression.

We believe that there is a need to develop a stepwise sequential approach for a more cost-effective and applicable treatment modalities that will integrate different evidence-based therapies while taking into account patients' characteristics and needs. Similar to treatment modalities in advanced individualised medicine, we encourage clinicians to use their clinical judgment and to make decisions based on session-to-session feedback and continuous awareness of the patient's progress. Medication can be incorporated into each phase of treatment; however, this is not the focus of our model at this point. Our suggestion is preliminary, stating that more research needs to be done in order to determine the specific use of medication (see Fig. 1 for the outline of the model).

Step 1: BA or PST. The treatment process should begin with a time-limited focused therapy such as BA or PST. Since these treatments are brief, cost-effective and have proven to be successful for large depressed populations, it would be reasonable to use them as a first line of treatment.

Step 2: CBT, IPT, EFT or STDP: In case of non-response, we suggest moving to the second phase – short-term treatments: CBT, IPT, EPT or STDP. Given the evidence from RCTs and meta-analyses, we believe that there is a great likelihood that these treatments will be equally effective and appropriate for patients who have failed to improve in briefer and more

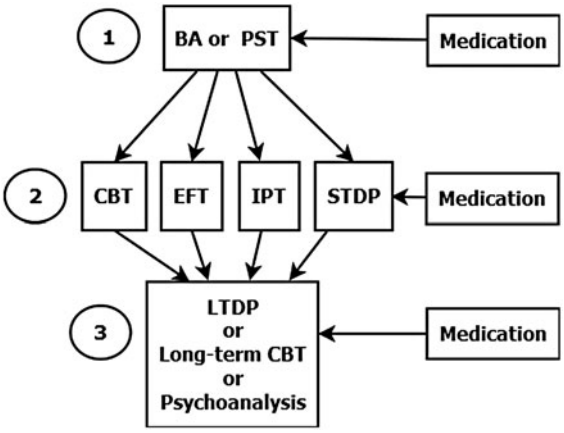

Fig. 1. A suggestion for an integrative stepwise sequential model for treatment of depression. *Note:* BA, behavioural activation therapy; PST, problem-solving therapy; CBT, cognitive-behavioural therapy; IPT, interpersonal therapy; EFT, emotion focused therapy; STDP, short-term dynamic psychotherapy; LTDP, long-term dynamic psychotherapy.

symptom-focused treatments. There is, however, some evidence that specific subgroups of patients benefit more from specific treatments (Barber & Muenz, 1996; Sotsky *et al*. 2006; Barber *et al*. 2012; Beutler *et al*. 2012; DeRubeis *et al*. 2014). If replicated, these findings should be included in the model.

Step 3: LTDP or Long-term CBT: Complex patients, who suffer from chronic depression and have shown two treatment failures in steps 1 and 2, will be referred to long-term CBT or LTDP. This suggestion is based on the promising evidence supporting the efficacy of LTDP for complex patients who experienced treatment failures and impressive RCT findings showing high remission rates (80.1%) after 18 months of combined therapy (cognitive therapy + medication) (Hollon *et al*. 2014).

Important considerations

The suggested model should be adjusted according to the therapist's clinical judgment, the patient's preferences and progress and the limitations of the clinical settings (such as the availability of therapists from a specific approach). Additionally, we expect that computer-based treatments will be included in this model in the future, given the increasing evidence supporting their efficacy and their advantages (high cost-effectiveness and high accessibility to a range of populations).

Lastly, we expect that future adjustments will be applied to the model based on the accumulating evidence on moderators and predictors of treatment success. Some preliminary findings have shown that

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specific populations benefit from specific treatments (e.g., Barber & Muenz, 1996; Sotsky *et al*. 2006; DeRubeis *et al*. 2014). For example, Barber *et al*. (2012) found that depressed minority men (mostly African-American) benefited more from short-term supportive-expressive therapy than placebo or medication. We recommend that future studies focus on replicating these previous findings and identifying more significant factors affecting treatment success.

Summary and concluding remarks

So what do we know? We know that there is a fairly wide range of effective psychotherapies. We also know that these treatments are probably more or less equally effective and that they are better than no-treatment or other control conditions. However, we still do not know why these treatments are often ineffective or only partially effective for many patients. We do not know why so many depressed patients choose to drop out of treatment. We also do not know why in many cases patients who have shown partial or full remission experience relapse. Given what we know and what we still do not know, we suggest a possible alternative model, incorporating EBT, while taking into account patients' specific needs and circumstances.

We acknowledge that while our model may be useful and applicable to Western countries, it might not be as relevant to individuals in third world countries, or even those who reside in remote areas of Western countries who lack access to services and/or the financial resources needed. That being said, we also predict that as the effects of globalisation increase and many countries become more developed, the demand for treatments of depression will drastically increase. Thus, there is a need for researchers to break through the boarders of their own countries (especially in the USA and Europe, where most researchers are located) and develop more rigorous and extensive research focusing on treatments that could be applicable for larger and more diverse populations world-wide.

With a lack of availability of treatments in remote areas and in less developed countries, depressed patients are more and more likely to be prescribed medication, especially as many SSRIs have become generic, without ever being offered psychotherapy. Our concern is that while medication can be as effective as and cheaper than therapy, it does not teach the patient anything (e.g. Barber & DeRubeis, 1989). It does not help the patient to gain insight and self-understanding, reflect on emotional states, challenge thoughts and beliefs, develop more adaptive coping skills and behaviours, improve self-esteem and make changes in interpersonal relationships.

While we acknowledge that the future goals of psychotherapy research are challenging and ambitious, we believe that the ever-growing productivity of psychotherapy researchers around the world and the increasing interest of young students and professionals in the field of psychotherapy can indicate that our field will continue to be fruitful and successful in decades to come.

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Conflict of Interest

None.

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