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Innovative treatments for depression

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Abstract

A number of high intensity psychosocial interventions have been shown to be as efficacious as and more enduring than medications in the treatment of nonpsychotic depression. Moreover there have been important advances in the development of strategies to facilitate the selection of the best treatment for a given patient. However, the demand for services is too great to be met by conventional high intensity approaches alone. Some of the most exciting work in recent years has focused on the development of low intensity approaches that can provide benefit to large numbers of people in a cost-effective fashion.

Introduction

The last several years have seen important innovations in the treatment of depression. We have learned more about established interventions (particularly with respect to how to select the best treatment for a given patient aka personalized or individualized approaches) and novel interventions (or new uses for established interventions) have been developed and evaluated. Perhaps the most exciting developments have come in the area of low intensity strategies that aim to deliver therapies with far shorter support time from the practitioner such as computerized therapy and bibliotherapy (printed manuals). The evidence base for such approaches continues to develop, and there are suggestions of equal outcomes to traditional so-called high intensity psychotherapy approaches delivered as one hour sessions by an expert practitioner, often over 12-20 sessions. We review these developments in turn.
We consider three types of relative outcomes.\textsuperscript{1} \textit{Efficacy} refers to whether an intervention has a causal effect and can be inferred via clinical trials whenever a treatment is compared to a control group and found to be better than its absence. \textit{Specificity} refers to whether an intervention is more efficacious than the generic effects of simply going into treatment such as the general effects of feeling listened to, receiving support, mobilization of hope and the establishment of a working alliance. \textit{Superiority} refers to whether an intervention is actually better than alternative “active” interventions such as another talking therapy or medication. As we shall see, most of the existing psychosocial interventions are efficacious (they are better than their absence) and some may be specific (they have active mechanisms that rise above the nonspecific benefits of simply going into treatment). Whether any one is superior to one another is an ongoing matter of contention\textsuperscript{2} and allegiance effects loom large in individual comparisons.\textsuperscript{3} We also note that there is an asymmetry in the field; medications cannot be approved for sale unless they have demonstrated specificity (they must exceed placebo controls in order to be marketed) whereas it is perfectly reasonable for therapists to charge for psychosocial interventions that may provide little more than nonspecific support and the promise of confidentiality from a sympathetic listener.\textsuperscript{4} In fact, the major portion of the acute effects produced by interventions for depression are a consequence of these nonspecific processes,\textsuperscript{5} although as we shall see some of the cognitive and behavioral interventions have enduring effects not found for medications that last beyond the end of treatment.\textsuperscript{6}

\textbf{Established High Intensity Interventions:}

Cognitive behavioral therapy (CBT) remains one of the best established of the existing treatments for unipolar depression. Although labeled as a unitary approach, multiple different minor modifications of the general model have been developed and evaluated. CBT has been shown to be as efficacious as antidepressant medications with each superior to pill-placebo in the treatment of patients with more severe depressions.\textsuperscript{7} This finding was confirmed in a recent individual patient level meta-analysis involving over 1700 patients treated in randomized controlled trials (RCTs) comparing the two monotherapies.\textsuperscript{8} CBT has been criticized by some as lacking long-term follow-up, however CBT has an enduring effect after treatment termination not found for antidepressant medications\textsuperscript{9}. There are indications that this enduring effect might even be superior prior to continuing remitted patients on antidepressant medications.\textsuperscript{10} Adding CBT appears to produce a modest 10\% increment in rates of recovery over medication alone, but this increment is heavily moderated; non-chronic patients with more severe depressions showed a rather large 30\% increment, whereas non-chronic patients with less severe depressions did not need this addition and chronic patients regardless of severity did not benefit from it (incremental benefits were negligible for each of these latter two groups).\textsuperscript{11} DeRubeis and colleagues have developed a novel strategy for generating algorithms that can identify the best treatment for a given patient. Application of this personalized advantage index (PAI) to a recent RCT indicated that about a quarter of the patients randomized to each monotherapy (CBT or antidepressant medications) would have done better if they had received the other and that overall outcomes would have been improved by as much as the advantage of antidepressant medications over pill-
placebo if each patient had received optimal treatment. The PAI can be applied to any treatment and could be used to improve the efficiency of health care delivery and to increase the power and specificity of tests of mechanism. However, this specialist high intensity CBT approach is maximized when manualized and delivered by trained and competent practitioners who receive ongoing supervision. When delivered in robust ways high efficacy in terms of recovery are achieved however results can be more disappointing where services are introduced without a focus on a consistently delivered service. There is increasing interest as to whether and how CBT can be delivered via low intensity interventions such as books (bibliotherapy) and online (see later).

**Behavioral Activation** represents a partial return to the principles of behavioral medicine as developed within the 1960’s and 1970’s and extends the model to include added concepts such as choosing to do activities that the person values, as well as activities that provide a sense of pleasure, achievement and closeness to others. It also emphasizes the importance of engaging in routine/mundane activities such as washing clothes, household chores and self-care as important ways of preventing further problems from developing. The focus is still on behavior more than on cognition and instead emphasizes engagement with potential reinforcers in the environment. Avoidance is a key target for change and the model argues that when someone is distressed it is a relief not to have to do usual activities. However, the less people do, the worse they feel and the worse they feel the less they do, contributing to a vicious cycle of avoidance, which is the target for change.

In a study conducted at its home institution, Behavioral Activation was as efficacious as antidepressant medications and superior to both CBT and pill-placebo among patients with more severe depressions and as enduring as CBT (with each superior to prior antidepressant medications) following treatment termination. A subsequent study conducted in Iran found Behavioral Activation superior to antidepressant medications (albeit at about half the maximum dosage) and another in the United Kingdom found it superior to treatment as usual. Trials are currently underway comparing Behavioral Activation to CBT in primary care settings in the UK and rural India and an as yet unpublished trial indicates that it reduces depressive symptoms with no risk of side effects in antenatal depressed women (S Dimidjian, November 29, 2015, personal communication). Behavioral Activation appears to be less complicated to learn than CBT and if its apparent enduring effect proves to be robust it may supplant that more established intervention. It is possible to train non-specialist nurses to deliver Behavioral Activation and as with CBT, it can be successfully delivered in both high intensity and low intensity ways. Again, there is increasingly a focus on delivering Behavioral Activation approaches in low intensity ways via the use of worksheets, books and online therapies with high success.

**Mindfulness-based Cognitive Therapy (MBCT)** involves an integration of meditation training with cognitive therapy that is often provided in a group format. MBCT is well established as a preventive intervention and is often provided to patients who have first been brought to remission with antidepressant medications or other interventions. MBCT is currently recommended to prevent relapse in people who have had 2+ episodes of depression, however there is a lack of evidence as to whether mindfulness approaches can aid milder depression or anxiety. Its mindfulness component may carry less stigma.
Acceptance and Commitment Therapy is one of the newer “third wave” behavior therapies (along with Behavioral Activation and MBCT) that emphasize context and experiential aspects of psychological experience. It was developed to focus more on complicated long-standing treatment resistant disorders and has not been as often applied to patients with diagnosed depressions although change in the symptom of depression often has been assessed across time. A recent meta-analysis found nearly 40 trials that assessed depression across the course of treatment in samples with a variety of different disorders; in those trials, Acceptance and Commitment Therapy produced large within-group reductions in symptoms and moderate reductions relative to minimal treatment controls (but not active controls). For example, only one study (conducted in Iran) focused on the treatment of patients who met criteria for major depressive disorders and cell sizes in that trial were quite small. Although not as often studied as the other interventions with respect to diagnosed depression, it would appear that existing findings are promising with respect to efficacy if not specificity.

Interpersonal Psychotherapy (IPT) has, until recent years, had one of the most consistent records of efficacy in controlled trials, demonstrating both efficacy and specificity across a number of trials. That may be in part due to the fact that it has not been all that widely adopted and as a consequence most of the controlled trials were done by advocates expert in its implementation. That has changed somewhat in recent years. A trial coming out of New Zealand found that IPT was less efficacious that CBT in the treatment of patients with more severe depressions or personality disorders and another trial done in Canada found IPT less efficacious than antidepressant medications. On the other hand, an even more recent trial from the Netherlands found no differences between IPT and CBT with indications of differential response (moderation) on the part of different patients. At this time it seems fair to say that IPT remains one of the best established treatments for depression although it is still not widely practiced outside of certain areas.

Dynamic Psychotherapy remains one of the most widely practiced but least evaluated psychosocial interventions. In the last decade there has been an increased emphasis on brief interventions, often characterized by manualized approaches and focused goals. There have been two recent trials worth noting. In the first, Supportive-Expressive Therapy, a form of brief dynamic psychotherapy, did not differ from antidepressant medications (sertraline with non-responders switched to venlafaxine at mid-treatment) or pill-placebo across sixteen weeks of treatment. Within the larger sample, black men did better in Supportive-Expressive Therapy than they did in either of the two pill conditions.
and white women did better in either active intervention than they did in pill-placebo. In a separate trial conducted in the Netherlands, short-term dynamic psychotherapy did not differ from CBT with noninferiority shown for the continuous measures of depression but not for the somewhat disappointingly low categorical remission rates (22.7% overall). It is not clear what conclusions can be drawn from these studies. On the one hand, dynamic psychotherapy was not inferior to two of the best-established interventions in the field (antidepressant medications and CBT), but on the other hand, neither study demonstrated either efficacy or specificity with what were essentially null findings. If dynamic psychotherapy were a novel medication the FDA would not have counted either as a positive indication sufficient for marketing. The first trial did include a nonspecific control condition, but antidepressant medications only exceeded pill-placebo in about half the trials submitted to the FDA to win marketing approval for more recent serotonergic medications and CBT in the second trial was conducted by a group with no prior track record with that approach. Neither consideration inspires confidence in the generalizability of the comparisons.

As an overview, typically evidence-based interventions share three characteristics; they have a clear structure, focus on problems relevant to the person and build on a relationship with a practitioner. This relationship has traditionally been extensive in terms of time and frequency of sessions (up to one hour sessions for 12-20+ weeks). So, a typical mindfulness course recommends 26 hours of therapy, and over 20 hours for treatment resistant depression. However, can a proportion of people recover equally well with shorter and more focused interventions?

**Established Low intensity interventions**

In clinical services there is often a challenge as to how to offer an effective intervention that is evidence based, well delivered and also cost-effective. In paid-for settings where there is often a limit to the number of sessions it becomes especially important to test interventions that potentially can be delivered in shorter, more focused ways, and with less practitioner time overall; hence low intensity in contrast to the high intensity (longer) traditional ways of delivering therapies. Bennett-Levy et al provides an overview of the low intensity approaches.

Three key components are emphasized in low intensity delivery:

1) **Therapeutic model:** Low intensity approaches have been developed and tested across an increasing range of disorders including depression, anxiety, panic, pain and fatigue and more. The majority of evaluated interventions to date have used the CBT approach, reflecting its structured approach and psychoeducational skills-based content that makes it especially appropriate for low intensity delivery. Increasingly MBCT, Acceptance and Commitment Therapy and Behavioral Activation approaches also are becoming available via low intensity interventions as well. Other approaches like brief psychodynamic therapy also can be delivered in this way. CBT-based resources (both book and online) are more effective at treating depression than approaches using psychoeducation alone.
2) Modality of delivery: Low intensity delivery has at its heart the concept that resource materials deliver key components of the therapy. This might include delivery via the media of books (bibliotherapy), and computers (for example computerized CBT- cCBT). Both approaches lead to equivalent outcomes\(^{44}\). Online approaches can provide scalability to encompass large number of people; also members of the public are more likely to endorse online approaches than book-based approaches, and both are seen more positively when offered with therapist support (i.e. as guided self-help) rather than unsupported (unguided)\(^{45}\). Some wider issues are also important when making judgements about what resources to choose to use. Both books and online resources vary significantly in terms of accessibility and readability and the typical reading age required for bibliotherapy approaches excludes significant numbers of potential readers\(^{46}\). It has been suggested that a learning assessment should occur as well as a clinical assessment to identify choice of low intensity resources\(^{47}\).

3). Amount and type of support: For depression, the efficacy of CBT-based (self-help) resources improves significantly when accompanied by support from a practitioner. It appears this support can be delivered effectively by either experts or non-experts in CBT, and the focus of the support does not need to include additional therapy components\(^{44}\). Support contacts play a key role in helping encourage and motivate the patient to use the resources, and help overcome blocks and low motivation in applying what is learned. It appears there is no difference in outcome when support is delivered face-to-face or by telephone. Online support (email or chat) is likely to be as efficacious. It is uncertain whether text-based chat is as effective, although it may have a role in reminding users to read or test out resources.

Does it work?
An overview of studies suggests that computer-delivered and book-delivered CT appear equally effective and modality selection should be informed by patient choice\(^{44}\). A review of studies comparing low and high intensity interventions found equivalent outcomes in both the short and longer term\(^{48}\). There are many uncertainties however and a recent large, well-conducted study with an active control found no advantage of cCBT (free or licensed) over GP usual care\(^{49}\). However that study provided little in the way of active support for the packages perhaps explaining the result.

Controversies and challenges in low intensity delivery:
1) Who provides the support? A key issue in low intensity working is whether fidelity to the underlying evidence-based model can be attained. Critics question whether such approaches provide only a cheap and poorer delivery. This is not borne out by the data, or national treatment guidelines. Secondly, it is not fully clear whether some subgroups of people do better with more flexible support from a skilled and trained practitioner, rather than a generic support worker. In practice, at least in the UK, a majority of accredited CBT (high intensity) specialists also supplement their work with self-help resources\(^{50}\). Trials are needed to clarify if this added expertise and knowledge of the CBT model leads to improved outcomes. Provisional data\(^{44}\) suggests not, however this review examined the combined results of studies rather than identifying whether specific groups of patients require added input (for example more complex or chronic presentations).
2) Which patients do well or badly with low intensity approaches? Many clinicians view CBT-based resources such as cCBT as being less effective than seeing a specialist practitioner. They identify patients who might do well as being milder in presentation. This view is not supported by findings of larger benefits in clinical samples compared to those who are less unwell. Also, severity did not predict who failed to engage with or benefit from low intensity interventions. It is also unclear whether age affects outcomes.

Conclusions:
It is an interesting time for evidence-based psychological therapies. The evidence base for traditionally delivered high intensity interventions is now established, reflecting benefits comparable to antidepressant medication across acute treatment with a long-term enduring effect (at least for CBT and possibly Behavioral Activation) not found for medications. Attention has turned to whether similar benefits can be gained by delivering the same interventions in shorter and more focused ways. There is a growing evidence base suggesting that at least for CBT and Behavioral Activation, low intensity interventions can be delivered effectively. However, for both high and low intensity intervention, the challenge now is the transition from the good results found in well controlled, manualized and supervised clinical trials, into everyday clinical services. Much more needs to be known about patient preference, how to engage people in ways they want to work, and how to offer an approach that is consistently delivered in high quality ways in order to maximize outcomes.

Four CME questions

1) Perhaps the major advantage that the cognitive and behavioral interventions have over antidepressant medications is that:
   a) they work faster than medications
   b) they are more robust in practice
   c) they are less expensive to provide
   d) they last longer than medications

2) One advantage that Behavioral Activation has over CBT is that:
   a) it is less complicated and easier to learn
   b) it has an enduring effect not found for CBT
   c) it produces fewer behavioral side effects
   d) it is less likely to generate stigma than CBT

3) Low intensity interventions for depression:
   a) Work best with people experiencing milder symptoms of depression
   b) Are best delivered with practitioner support
   c) Always use the CBT approach
   d) Show maximum benefit when delivered online

4) Low intensity interventions are effective when:
   a). Support is delivered face to face compared to by telephone
b). Longer and more sessions of support are offered
c). They are supported by non-mental health specialists
d). They contain a psychoeducational content
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