Consensus statement on defining and measuring negative effects of Internet interventions

Rozental, Alexander; Andersson, Gerhard; Boettcher, Johanna; Ebert, David Daniel; Cuijpers, Pim; Knaevelsrud, Christine; Ljótsson, Brjánn; Kaldo, Viktor; Titov, Nickolai; Carlbring, Per

Published in:
Internet Interventions

DOI:
10.1016/j.invent.2014.02.001

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

Internet Interventions 1 (2014) 12–19

Contents lists available at ScienceDirect

Internet Interventions

journal homepage: www.invent-journal.com/

Consensus statement on defining and measuring negative effects of Internet interventions

Alexander Rozental [a,*], Gerhard Andersson [b,c], Johanna Boettcher [d], David Daniel Ebert [e], Pim Cuijpers [f], Christine Knaevelsrud [d], Brjánn Ljótsson [g], Viktor Kaldo [c], Nickolai Titov [h], Per Carlbring [a]

[a] Division of Clinical Psychology, Department of Psychology, Stockholm University, Stockholm, Sweden
[b] Department of Behavioural Sciences and Learning, Swedish Institute for Disability Research, Linköping University, Linköping, Sweden
[c] Division of Psychiatry, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Department of Clinical Psychology and Psychotherapy, Freie Universität Berlin, Berlin, Germany
[e] Division of Clinical Psychology and Psychotherapy, Department of Psychology, Philipps University Marburg, Marburg Germany
[f] Department of Clinical Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
[g] Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[h] MindSpot Clinic, eCentreClinic, Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia

ARTICLE INFO

Article history:
Received 13 February 2014
Received in revised form 20 February 2014
Accepted 21 February 2014
Available online 3 March 2014

Keywords:
Internet interventions
Consensus statement
Negative effects
Mental health

ABSTRACT

Internet interventions have great potential for alleviating emotional distress, promoting mental health, and enhancing well-being. Numerous clinical trials have demonstrated their efficacy for a number of psychiatric conditions, and interventions delivered via the Internet will likely become a common alternative to face-to-face treatment. Meanwhile, research has paid little attention to the negative effects associated with treatment, warranting further investigation of the possibility that some patients might deteriorate or encounter adverse events despite receiving best available care. Evidence from research of face-to-face treatment suggests that negative effects afflict 5–10% of all patients undergoing treatment in terms of deterioration. However, there is currently a lack of consensus on how to define and measure negative effects in psychotherapy research in general, leaving researchers without practical guidelines for monitoring and reporting negative effects in clinical trials. The current paper therefore seeks to provide recommendations that could promote the study of negative effects in Internet interventions with the aim of increasing the knowledge of its occurrence and characteristics. Ten leading experts in the field of Internet interventions were invited to participate and share their perspective on how to explore negative effects, using the Delphi technique to facilitate a dialog and reach an agreement. The authors discuss the importance of conducting research on negative effects in order to further the understanding of its incidence and different features. Suggestions on how to classify and measure negative effects in Internet interventions are proposed, involving methods from both quantitative and qualitative research. Potential mechanisms underlying negative effects are also discussed, differentiating common factors shared with face-to-face treatments from those unique to treatments delivered via the Internet. The authors conclude that negative effects are to be expected and need to be acknowledged to a greater extent, advising researchers to systematically probe for negative effects whenever conducting clinical trials involving Internet interventions, as well as to share their findings in scientific journals.

1. Introduction

During the last two decades research has provided increasing evidence for the use of Internet interventions (Andersson et al., 2013). Numerous clinical trials have demonstrated the efficacy of treatments delivered via the Internet for a wide range of psychiatric conditions, e.g., depression (Wagner et al., 2014), social phobia (Andrews et al., 2011), panic disorder (Carlbring et al., 2006), generalized anxiety disorder (Titov et al., 2009), insomnia (van Straten et al., 2013), tinnitus (Nyenhuis et al., 2013), pathological gambling (Carlbring and Andersson, 2006), comorbid anxiety disorders (Johnston et al., 2013), irritable bowel syndrome (Ljótsson et al., 2011), among others. Until recently, Internet interventions have mainly involved the use of cognitive behavior therapy. However, current research also indicates that psychodynamic psychotherapy can be delivered as guided self-help with

* Corresponding author at: Division of Clinical Psychology, Department of Psychology, Stockholm University, Frescati Hagväg 8, Stockholm 106 91, Sweden. Tel.: +46 8 16 38 71; fax: +46 8 15 93 42.
E-mail address: alexander.rozental@psychology.su.se (A. Rozental).

http://dx.doi.org/10.1016/j.invent.2014.02.001
2214-7829/

promising results for both depression (Johansson et al., 2013c) and anxiety disorders (Andersson et al., 2012a; Johansson et al., 2013a), as well as guided physical activity (Ström et al., 2013), and problem-solving therapy (Warmerdam et al., 2008). Internet interventions are assumed to have several advantages over face-to-face treatment, e.g., higher cost-effectiveness, increased access to evidence-based treatments, and greater opportunity to reach patients on remote locations (Carlbring and Andersson, 2006). Hence, it is reasonable to assume that Internet interventions will become a common alternative to face-to-face treatments in order to meet an increasing demand of mental health services (Johansson et al., 2013b; Kohn et al., 2004).

Because research on Internet interventions has primarily focused on examining its effectiveness little is known about the occurrence or characteristics of negative effects (Boettcher et al., 2014). However, this is far from unique in its field and reflects a major shortcoming of psychotherapy research in general (Nutt and Sharpe, 2008). Investigations on negative effects have primarily dealt with so called fringe psychotherapies or potentially harmful therapies, e.g., rebirthing, scared straight interventions, critical incidence stress debriefing, and recovered-memory techniques, whilst paying less attention to the potential negative effects of evidence-based treatments (Berk and Parker, 2009; Beyerstein, 2001). In recent years, the importance of exploring negative effects of established treatments has also been proposed in order to avoid the possibility of some patients getting worse despite receiving best available care (Barlow, 2010). Similarly, Foulkes (Foulkes, 2010) pointed out that any treatment with the potential of alleviating distress also carries with it the risk of evoking negative effects. In other words, therapists should be aware of the probability of inadvertently inducing negative effects during the course of treatment (Castonguay et al., 2010).

To what extent negative effects occur in psychotherapy is a topic of great debate (Boisvert, 2010). Bergin (Bergin, 1966) is often acknowledged as the first person to describe the possibility of a treatment producing negative effects, although earlier examples are mentioned in the literature, e.g., Mohr (Mohr, 1995) presents a complete review. Bergin (Bergin, 1966) examined several psychotherapy outcome studies and found that some patients consistently seem to deteriorate during treatment. Lambert (Lambert, 2007) has suggested that between 5 and 10% of all patients undergoing psychotherapy deteriorate, a number that also appears in clinical trials at different outpatient care settings (Hannan et al., 2005; Hatfield et al., 2010; Heins et al., 2010; Lambert et al., 2002). However, determining whether the negative effects are a consequence of treatment requires a comparison group to control for the natural course of the target problem (Dimidjian and Hollon, 2010). Also, deterioration may not be the only negative effect associated with treatment (Boisvert and Faust, 2002). Hadley and Strupp (1976) conducted a survey among researchers and therapists on the prevalence and definition of negative effects, resulting in a summary of possible detrimental effects of psychotherapy ranging from low self-esteem to becoming dependent on the therapist. They proposed a tripartite model in which negative effects are assessed from the perspective of the patient, the therapist, and society (Strupp and Hadley, 1977; Strupp et al., 1977). Lilienfeld (2007) made a similar distinction, stating that any intervention might be experienced as negative by the patient, e.g., assertiveness training or exposure in vivo, even though it is believed by the therapist to be beneficial in the long run. Likewise, the outcome of psychotherapy in terms of symptom reduction, increased well-being, and greater independence does not necessarily represent a positive result for a partner or relative, who may have been enjoying secondary benefits from the patient's disorder (Crown, 1983; Kottler and Carlson, 2003; Stuart, 1970). Furthermore, Dimidjian and Hollon (2010) suggested that treatment nonresponse should also be considered negative, as it could have prevented the patient from receiving more adequate care, or experiencing spontaneous remission, prolonging or even increasing the distress. In sum, determining what constitute negative effects of treatment depends on both the perspective from which the treatment is evaluated (e.g., patient, therapist, significant other, or society) and what is regarded as a favorable outcome (Foa and Emmelkamp, 1983; Mays and Franks, 1980).

In comparison to psychotherapy research, monitoring negative effects is required when evaluating the benefits and risks of pharmacological medication (Wysowski and Swartz, 2005). In order to introduce a new drug, as well as to surveil possible adverse events of an existing drug, investigating negative effects is essential and regulated by the pharmaceutical industry, government agencies, as well as international committees, e.g., World Health Organization (Curtin and Schulz, 2011). Assessment is often based on benefit–risk ratios, quantifying the numbers of favorable outcomes achieved for each additional unfavorable outcome (Willan et al., 1997). However, the usefulness of this framework is limited to clinical trials using a single outcome measure and can only distinguish one type of adverse event at a time (Willan et al., 1997). Methods for exploring other possible negative effects have therefore been suggested (Curtin and Schulz, 2011). Kalachnik (1999) provides a review of the most common monitoring procedures of negative effects of pharmacological medication: measurements can be administered on an organizational level, e.g., retrospective data collected from patient journals or the use of laboratory methods, rating scales and checklists for specific negative effects or negative effects in general, and applied individual methods adapted from behavioral psychology, e.g., examining the frequency, intensity, and duration of a target behavior. Negative effects can also be classified as either predictable reactions or unexpected or idiosyncratic reactions (Edwards and Biriell, 1994). Kalachnik (1999) points out that no method will detect all negative effects and that it is advised to use a combination of measures when conducting clinical trials or examining negative effects in clinical practice. Similar to psychotherapy research, the medical literature is not uniform in terms of its terminology, resulting in the use of different definitions to describe the same phenomenon (Edwards and Biriell, 1994). The recommendation is therefore to report all negative effects of a drug even though it might not be related to the medication in use (Goldmann et al., 1995). This is deemed important as it could facilitate hypothesis generation, further investigation, and possibly the need for precautionary measures (Kalachnik, 1999).

Recently, the need for expanded monitoring of negative effects in clinical trials of psychotherapy has been discussed, resulting in different suggestions on how to define and measure negative effects (Peterson et al., 2013). Linden (2013) presented a comprehensive checklist dividing negative effects into different categories. This involves events and reactions unrelated to treatment, nonresponse, deterioration of illness, therapeutic risks and contraindications, and negative effects attributable to the treatment per se. Negative effects are however consistently defined as side effects, a concept primarily used in research of pharmacological medication (Kalachnik, 1999), but has previously been advised by Mays and Franks (1985) not to be used in psychotherapy research as it does not reveal whether the side effects are positive or negative. Furthermore, malpractice reactions are also included, although some argue that they should be distinct from negative effects of evidence-based treatments (Berk and Parker, 2009). On the one hand, Linden's (2013) checklist has a number of advantages in terms of detecting negative effects of treatment as it incorporates the perspectives of both the patient and the therapist, as well as deterioration on validated outcome measures. Parker et al. (2013) on the other hand, have proposed a questionnaire intended to survey the experiences of patients undergoing or having completed psychotherapy. In their research, negative effects were evaluated in relation to premature treatment termination, and then quantified and categorized according to recurrent themes. Results indicated that ineffective treatment, external factors (e.g., lack of money or time, and current work situation), and a dislike of the therapist or the therapeutic orientation were common reasons to terminate treatment prematurely. In particular, negative therapeutic alliance was deemed an important mechanism related to negative effects, but also non-specific therapeutic factors, e.g., relocation of therapist and interfering

personal commitments (Parker et al., 2013). Although a valuable source of information, determining negative effects solely on the basis of self-reports does not reveal whether it affects treatment outcome, making it difficult to conclude whether the experiences of the patient have a long term negative effect (Dimidjian and Hollon, 2010).

Despite the many complexities surrounding the investigation of negative effects, further research is needed in order to prevent patients from encountering adversities and experiencing deterioration caused by treatment (Barlow, 2010). However, because no consensus currently exists regarding the definition and procedures of measuring negative effects the field lacks a common ground to guide its research (Peterson et al., 2013). Dimidjian and Hollon (2010) recently suggested that methods from both qualitative and quantitative research should be used, ranging from descriptive case studies to randomized controlled trials. Self-reports from individual patients could for instance provide a rich narrative in which possible relationships between an intervention and negative effects are explored. Contrasting deterioration rates between randomized conditions in a clinical trial could on the other hand reveal if negative effects are more common in the presence or absence of treatment, as well as uncovering possible patient characteristics associated with negative effects (Dimidjian and Hollon, 2010). Even though these guidelines were initially intended for face-to-face treatment, they can also be modified and used in research of Internet interventions. Since most treatments delivered via the Internet are derived from face-to-face treatments there is a reason to believe that they share some commonalities, both in terms of positive and negative effects. It is also plausible that there are negative effects unique for Internet interventions. The treatment could for instance be experienced as negative by some patients when unaccompanied by a therapist, particularly in the event of relapse. Similarly, technical issues and difficulties understanding the treatment rationale might interfere with progress and result in dropout. Understanding the occurrence and characteristics of negative effects in Internet interventions is thus important, and could lend valuable information on how to prevent negative effects from occurring. In addition, investigating both positive and negative effects of Internet interventions is important in order to fulfill the ethical and legal considerations of conducting treatments via the Internet (Dever Fitzgerald et al., 2010). Although the suggestions of Peterson et al. (2013), Linden (2013), and Parker et al. (2013) are useful, it is essential to extend the discussion of negative effects to the field of Internet interventions. The current paper therefore seeks to explore ways of defining and reporting negative effects in Internet interventions in order to form a consensus and provide researchers with recommendations that could be used in clinical trials.

2. Material and methods

In order to form a consensus statement ten leading experts in Internet interventions were invited by the first author to share their thoughts on the topic of negative effects and endorse the results, all of whom accepted participation. The experts were selected based on their extensive experience of conducting clinical trials in different fields of Internet interventions, including outpatient clinics and research facilities, and a number of psychiatric conditions. The Delphi technique was employed to facilitate a dialog between participants and reach an agreement (Danial-Saad et al., 2013; Spinelli, 1983). This technique was originally developed to enhance forecasting and decision making of interacting groups, i.e., considering multiple sources of information and improving creativity, while preventing conformity and social inhibition. The process usually involves four key elements: anonymity, iteration, controlled feedback, and a statistical aggregation of group response (Danial-Saad et al., 2013; Rowe and Wright, 1999). However, due to the qualitative nature of the current investigation, the use of a statistical aggregation was not appropriate, and a summary of common themes was developed instead. First, the participants were asked to complete an online survey anonymously regarding negative effects in Internet interventions adapted from Hadley and Strupp (1976) (see Appendix A). Second, the responses were compiled and sent out for review, allowing the participants to comment on each other anonymously. Third, the result from this procedure was used to draft a consensus statement, i.e., the current paper, which the participants were requested to examine and modify before it was submitted for publication. This enabled additional information to be provided throughout the process of reaching an agreement, and allowed revisions of previous statements. A similar approach was used to establish guidelines for executing and reporting Internet intervention research, albeit without the aid of the Delhi technique (Proudfoot et al., 2011). The outcome of the consensus statement is presented below summarizing the issues in need of consideration when monitoring and reporting negative effects in Internet interventions, followed by recommendations that will guide future research.

3. Results

3.1. The problem of negative effects

Clinical trials investigating negative effects of Internet interventions is currently scarce, and only recently has the issue been acknowledged in the research (Boettcher et al., 2014). Prior knowledge regarding its occurrence and characteristics is therefore lacking, as well as recommendations on monitoring procedures and the process of reporting the results. Consequently, there is still insufficient evidence to talk about a problem of negative effects, even though it has been suggested that a proportion of all patients undergoing face-to-face treatment deteriorate (Lambert, 2007). However, the lack of knowledge does not imply that negative effects are absent in Internet interventions, rather that more research is warranted in order to determine its prevalence and implications, as well as to improve the understanding of the mechanisms underlying negative effects. A greater awareness of the possibility that negative effects might occur is therefore important, and different measures for monitoring negative affects should be applied when conducting clinical trials of Internet interventions.

Recommendation: Researchers need to be mindful of the fact that some patients could experience adverse events and deteriorate during treatment, and systematically probe and report negative effects when performing clinical trials of Internet interventions. This would increase the knowledge of negative effects, and hopefully result in the implementation of precautionary measures. The following aspects have been identified as particularly important when examining negative effects in Internet interventions and need to be recognized.

3.1.1. Similarity

Internet interventions share many similarities with face-to-face treatments in terms of the methods and techniques being used. Most treatments are for instance adopted from evidence-based treatments and use the same treatment manuals for different psychiatric conditions. Admitting that negative effects exist and could pose a problem in face-to-face treatment also assumes its presence in Internet interventions, which conveys the relevance of conducting further investigation regardless of treatment format. Negative effects should therefore be expected and considered in research of Internet interventions, and could presumably further the understanding of negative effects in general.

3.1.2. Differences

Despite a great overlap, the context in which Internet interventions is performed can also be associated with a unique set of negative effects for some patients undergoing treatment. Unguided self-help may for instance be related to a greater risk of misunderstanding the treatment rationale. Inadequate delivery of certain interventions may also contribute to the experience of adverse events, e.g., performing behavioral experiments that are not carefully planned, or exposure in vivo

that is not properly executed. In comparison to face-to-face treatment, Internet interventions lack the same degree of control and possibility to address adherence or comprehension of treatment content. Also, the communication between patient and therapist is often limited, i.e., lack of feedback, and non-verbal stimuli, which might be a potential source of misinterpretation and making it more difficult to correct potential errors. However, Internet interventions may also comprise several advantages that might be beneficial for some patients, e.g., increased opportunity to contact the therapist during treatment, and a high degree of structure. Although some negative effects might be inherent in Internet interventions, it is also reasonable to assume that there are aspects that prevent some of the negative effects that could be associated with face-to-face treatments, warranting further research on the differences of negative effects between face-to-face treatment and Internet interventions.

3.1.3. Causality

Recognizing the occurrence of negative effects does not imply a causal relationship between the interventions in use and the adversities or deterioration experienced by the patient. Negative effects could for instance be caused by circumstances unrelated to treatment, e.g., interpersonal problems, financial difficulties, or vocational issues, as well as the natural course of the target problem (Dimidjian and Hollon, 2010). Understanding the mechanisms underlying negative effects motivates an investigation of causality, similar to studying the possible links between the properties of a certain drug and its negative effects in pharmacological research (Kalachnik, 1999). Thus, it is necessary to compare treatment conditions in randomized controlled trials in order to determine the prevalence and characteristics of negative effects, i.e., guided versus unguided self-help, and treatment versus no treatment. Similarly, differentiating negative effects of Internet interventions from face-to-face treatment could also be informative, highlighting common factors that are related to negative effects.

3.2. Classifying negative effects

Negative effects are defined differently depending on the scope of the research and the terminology being used, varying from deterioration and nonresponse, to the emergence of novel symptoms and social implications. Consequently, research on negative effects can often be interpreted in a number of ways, obfuscating the results and the understanding of underlying mechanisms (Edwards and Biriell, 1994; Peterson et al., 2013). Using a more coherent classification may promote the investigation of negative effects by providing a clear set of definitions that would guide the research forward.

3.2.1. Recommendation

Using a mutual terminology would facilitate monitoring and reporting of different types of negative effects that occur during treatment. The following definitions have been adopted from research of negative effects in face-to-face treatment (Linden, 2013), and researchers are advised to use these as a uniform classification for defining negative effects in Internet interventions.

3.2.1.1. Deterioration. Deterioration is defined as worsening of target symptoms and monitored by a validated outcome measure or behavioral measure, i.e., an increase of symptom severity, or increased frequency of intrusive thoughts. In order to distinguish temporary from enduring deterioration, consecutive measures and follow-up are also recommended, e.g., from pre- to post-treatment, weekly during treatment, and from post-treatment to follow-up.

3.2.1.2. Adverse events. Adverse events consist of negative events probably emerging from treatment and perceived as adverse by the patient, causing deterioration of target symptoms and/or negative experiences that extends beyond the completion of treatment, e.g., increased anxiety during interoceptive exposure, or being embarrassed by performing assertiveness training. Adverse events could reveal negative effects that are directly attributable to treatment, providing researchers with information on possible mechanisms underlying negative effects.

3.2.1.3. Severe adverse events. Severe adverse events are composed of negative events that occur during treatment and result in deterioration of target symptoms and/or adverse reactions requiring some form of high intensity treatment, e.g., misuse of alcohol or drugs, deliberate self-harm, and suicidal ideation or attempts. Because of the risks involved, severe adverse events should always be surveiled and reported regardless if they are deemed related to treatment or not.

3.2.1.4. Novel symptoms. Novel symptoms consist of the emergence of new psychological symptoms, unrelated to the symptoms targeted in treatment, which may or may not be associated with treatment, e.g., occurrence of insomnia during treatment of social anxiety, or decreased self-esteem during treatment of panic disorder. Similar to adverse events, novel symptoms could provide valuable information on negative effects that would otherwise go unnoticed, but differs from adverse events as novel symptoms should be unrelated to the symptoms targeted in treatment.

3.2.1.5. Dropout. Dropout concerns the number of patients choosing to end treatment prematurely. Early termination can be related with deterioration of target symptoms, nonresponse, and/or experiencing adverse events, presumably related to treatment, e.g., increase in symptom severity, or demoralization. Examining its occurrence in different treatment conditions as well as compared to face-to-face treatment could in turn help researchers investigate what factors are associated with higher dropout. However, if feasible, determining the reason for dropout is advised as it may also be related to a decrease in symptom severity, i.e., some patients might experience relief after a short period of time, perceiving more treatment as redundant.

3.2.1.6. Nonresponse. Nonresponse is characterized by the lack of a predicted positive effect on target symptoms, possibly attributable to treatment, resulting in status quo, demoralization and discouragement to seek help elsewhere, i.e., absence of any treatment effect. However, further exploration is required in order to distinguish the reason for reason and characteristics of the nonresponse, i.e., some patients might have deteriorated without treatment, or external factors might be responsible for the nonresponse, e.g., bereavement, or other social stressors.

3.2.1.7. Unwanted events. Unwanted events are defined as all events experienced as negative by the patient during treatment, which may or may not be related to the interventions being used, and does not necessarily influence treatment outcome, e.g., issues related to the treatment content, increased anxiety during exposure in vivo, and frustration caused by technical issues. Unwanted events do not provide any etiological assumptions, but could facilitate an understanding of what negative effects might be associated with treatment.

3.3. Monitoring negative effects

The investigation of negative effects can be pursued in multiple ways depending on the measures and routines being involved. Assessment could rely solely on validated outcome measures in order to determine deterioration, e.g., exacerbation of social anxiety from pre- to post-treatment (Barlow, 2010). However, negative effects unrelated to an increase in symptom severity may also occur, and the experiences of negative effects might vary from patient to patient, warranting the use of additional monitoring procedures (Parker et al., 2013; Peterson et al., 2013). Self-reports, interviews, checklists, and open-ended questions could therefore be equally important when conducting research of negative effects in Internet interventions, identifying aspects that would have been difficult to distinguish with validated outcome

measures alone. In addition, comparing the occurrence and characteristics of negative effects between treatment conditions may also reveal important differences, e.g., greater incidence of negative effects in wait-list control compared to treatment.

3.3.1. Recommendation

As a minimum, researchers are advised to investigate negative effects using validated outcome measures in order to determine deterioration between pre- and post-treatment, and between different treatment conditions. Researchers are also recommended to report the number of patients who did not respond to treatment as well as the number of patients who deteriorated during treatment. Furthermore, researchers are urged to probe for negative effects via self-report measures administered at post-treatment, i.e., "did you experience any negative effects during treatment". The following monitoring procedures are put forward to facilitate future research of negative effects in Internet interventions.

3.3.1.1. Standard outcome measures. The use of validated outcome measures is considered a standard practice in order to determine the efficacy of treatment. Outcome measures are therefore already included in most clinical trials of Internet interventions, and do not require any additional monitoring procedures in terms of investigating deterioration. Hence, assessment of negative effects should at least be performed by comparing scores from pre- to post-treatment, as well as from post-treatment to follow-up, indicating whether an increase in symptom severity is temporary or enduring (Dimidjian and Hollon, 2010). In addition, researchers are also advised to investigate negative effects on a consecutive basis, involving measures administered weekly during treatment or wait-list control. Besides validated outcome measures for specific psychiatric conditions, more global assessments of functioning or well-being are also possible to use (Lindner et al., 2013) as well as behavioral measures where applicable (Haynes et al., 1997). Deterioration on any outcome measure could also be defined according to the criteria of reliable deterioration defined by Jacobson and Truax (1991). In this approach, a critical difference between pre- and post-score/post- and follow-up-score is defined taking into account the reliability of the instrument. When possible, researchers could apply standard critical differences, for instance as defined for the Beck Depression Inventory (Seggar et al., 2002).

3.3.1.2. Additional self-report measures. The nature of negative effects may differ between patients and treatment conditions, warranting the use of self-report measures (Parker et al., 2013). Probing for adverse events could for instance reveal social implications or subjective experiences which are difficult to detect using only validated outcome measures. Self-report measures could consist of open-ended questions at post-treatment or following wait-list control, but should be administered weekly where possible in order to detect negative effects which might otherwise be forgotten by the patient. It may also involve semi-structured interviews exploring the unique perspective of the patient, or standardized checklists addressing some of the most frequently occurring negative effects of Internet interventions.

3.3.1.3. Clinical interviews. Administering a clinical interview could reveal negative effects undetected by self-report measures, but which are still considered negative in terms of affecting long term outcome (Dimidjian and Hollon, 2010). For instance, patients undergoing treatment with guided self-help might become dependent on the therapist in order to manage their distress. Likewise, misunderstanding the treatment rationale may lead to difficulties employing or adhering to specific techniques, resulting in self-accusation and a greater risk of relapse. A clinical interview could therefore provide valuable information from the perspective of the therapist, and enable a comparison of negative effects across different viewpoints. In most research settings clinical interviews such as the Structured Clinical Interview for the DSM (SCID; First et al., 1997) are often administered at post-treatment in order to determine the proportion of patients no longer fulfilling the diagnostic criteria for the disorder under treatment. However, these standard interviews do not cover questions on potential negative effects. Researchers and clinicians should therefore add open questions concerning the occurrence of possible negative effects that might be related to treatment.

3.4. Factors associated with negative effects

The investigation of negative effects is scarce, even more so regarding possible underlying mechanisms that might contribute to its occurrence. Different suggestions have been proposed in psychotherapy research in general, mainly involving sociodemographic variables or comorbidity that could predict treatment outcome (Hofmann and Suvak, 2006; Steketee and Shapiro, 1995). However, more in-depth analyses concerning what factors may be associated with negative effects are currently lacking, preventing researchers from exploring ways of enhancing treatment procedures and averting negative effects from occurring. From a theoretical perspective several factors have been put forward as plausible explanations of negative effects, e.g., the therapeutic relationship, exaggerated expectations of treatment outcome, and interventions inherent to specific therapeutic orientations (Berk and Parker, 2009; Nutt and Sharpe, 2008). Further research of these and other relevant factors may provide evidence of the predictors and mediators of negative effects. However, there might also exist differences between face-to-face treatment and Internet interventions regarding the mechanisms contributing to negative effects, as well as between guided and unguided self-help, warranting an investigation of what factors seem to be more prevalent in what treatment condition, and to compare these results with findings from face-to-face treatment.

3.4.1. Recommendation

Investigating factors associated with the occurrence of negative effects is essential for developing strategies to reduce the risk for negative effects. There is currently insufficient knowledge concerning the underlying mechanisms that might contribute to negative effects, and whether this differs between Internet interventions and face-to-face treatment, or treatment conditions. Examining possible predictors and mediators of negative effects is therefore important, and could lead to improved treatment procedures that may decrease the number of patients experiencing adversities or deterioration. The following suggestions highlight some of the factors that are believed to be related with negative effects in treatment, and could be used to guide future research of Internet interventions.

3.4.1.1. Disappointment. Nonexistent or insufficient treatment progress can result in feelings of disappointment, particularly if the patient had high expectations of symptom relief prior to entering treatment. This might in turn be perceived as negative, leading to both demoralization and dropout. Furthermore, disappointment could also involve a set of beliefs regarding the treatment or the effort needed to change, in turn disrupting both compliance and the comprehension of the treatment rationale (Boisvert and Faust, 2002). However, because disappointment most likely reflects the patient's notion of treatment rather than the treatment in itself, it is reasonable to assume that disappointment occurs in face-to-face treatment as well as Internet interventions, even though the reason behind the disappointment might differ in character.

3.4.1.2. Deficient treatment. The lack of structure or deficient procedures surrounding the treatment could be an important factor responsible for negative effects, resulting in frustration, self-accusation, and an increased risk of dropout (Castonguay et al., 2010). Instead of recognizing defects inherent to the treatment per se, patients might attribute their difficulties to personal features or shortcomings and terminate treatment prematurely. Because Internet interventions do not contain the

same amount of guidance or feedback as face-to-face treatment, the quality of the content and the framework being used is more essential, highlighting the significance of providing treatments that are simple, accessible, and coherent.

3.4.1.3. Therapist factors. The therapeutic relationship is a significant predictor of treatment outcome in face-to-face treatment (Del Re et al., 2012), and is assumed to be true for Internet interventions (Bergman Nordgren et al., 2013). However, the research is currently inconclusive and the importance of the therapeutic relationship is somewhat unclear (Andersson et al., 2012b). On the one hand, guided self-help accompanied by a therapist may facilitate behavior change and help some patients overcome their distress to a greater extent. On the other hand, guided self-help might also be associated with misunderstandings and alliance ruptures, contributing to the occurrence of negative effects, perhaps more so for patients suffering from interpersonal difficulties or personality disorders. Negative effects could also be more evident in those cases where the therapist does not have adequate training, i.e., an untrained or lay therapist, and be affected by the often unreliable communication inherent in Internet interventions, resulting in insufficient feedback from the patient and difficulties adapting the therapeutic style in writing or via telephone or video. In other words, whether or not the therapeutic relationship is a common source of negative effects in Internet interventions, and more so in treatments delivered via the Internet than face-to-face treatment, is still unknown and warrants further investigation.

3.4.1.4. Therapeutic orientation. For the most part, treatments delivered via the Internet have mainly involved methods and interventions stemming from cognitive behavior therapy (Andersson et al., 2013; Mohr et al., 2013), even though clinical trials have been performed on other therapeutic orientations as well, e.g., psychodynamic psychotherapy (Johansson et al., 2013a, 2013b, 2013c), guided physical activity (Hoek et al., 2012; Ström et al., 2013), and problem-solving therapy (Warmerdam et al., 2008). Hence, there is still insufficient knowledge on whether negative effects differ in terms of their occurrence or characteristics between therapeutic orientations. The same situation is evident in face-to-face treatment, although some evidence suggest that there are no significant differences (Lambert, 2007). However, from a theoretical standpoint there might be specific methods and interventions that cause negative effects to a greater extent in the treatment of certain psychiatric conditions. Performing behavioral experiments and exposure in vivo is for instance associated with a temporary increase in distress, even though the long term outcome might be beneficial for the patient. This could potentially lead to greater dropout compared to other therapeutic orientations, particularly in Internet interventions where the patient may lack proper guidance to execute the necessary interventions and when feedback from the therapist is not always possible.

3.4.1.5. Patient characteristics. Different patients may receive different results of the same treatment, partly related to the influence of specific patient characteristics. Sociodemographic variables, health literacy, and comorbid disorders are for instance regarded as predictors of treatment outcome, both in treatments delivered via the Internet and face-to-face treatments (Andersson et al., 2008; Jorm, 2012; Nordgreen et al., 2012; Spek et al., 2008). Whether these are associated with negative effects is however unclear, but could reveal important patient characteristics contributing to the occurrence of adversities and deterioration. Some patients may prefer conventional treatment in front of guided self-help, partly explained by prior experience of using the Internet. Likewise, some patients might benefit more from a highly structured treatment without any assistance. Specific patients' characteristics may therefore facilitate or interfere with treatment, revealing what patients benefit the most from the interventions being used.

4. Conclusion

Internet interventions are becoming increasingly available and offer a great opportunity to alleviate emotional distress, promote mental health and enhance well-being (Emmelkamp et al., 2014). As an alternative to face-to-face treatment Internet interventions could provide more patients with treatments that are effective for a wide range of psychiatric conditions (Andersson et al., 2013; Carlbring and Andersson, 2006). However, despite rapid progress little is known about the possibility that some patients might deteriorate or encounter adverse events during treatment (Boettcher et al., 2014). Evidence from face-to-face treatments suggests that between 5 and 10% of all patients experience negative effects in terms of deterioration alone (Hannan et al., 2005; Hatfield et al., 2010; Lambert, 2007; Lambert et al., 2002). To what extent other types of negative effects exist is still unclear and a topic of great debate (Boisvert, 2010), even though it has been proposed that a number of adverse events occur and should be recognized during treatment, e.g., lower self-esteem, self-accusation, and becoming dependent on the therapist (Crown, 1983; Dimidjian and Hollon, 2010; Lilienfeld, 2007; Strupp and Hadley, 1977). It is also unknown what underlying mechanisms are associated with negative effects, and whether those differ between Internet interventions and face-to-face treatment. Because both share much in common in regard to the methods and techniques being used, it is highly likely that negative effects also afflict patients undergoing treatments delivered via the Internet. To comprehend to what degree negative effects exist in Internet interventions it is therefore important to conduct research that investigates its occurrence and characteristics. Similar to the requirements of evaluating the benefits and risks of pharmacological medication (Curtin and Schulz, 2011; Kalachnik, 1999; Wysowski and Swartz, 2005), research concerning treatments delivered via the Internet should monitor and report negative effects in order to live up to ethical and legal considerations (Dever Fitzgerald et al., 2010). The current paper invited leading experts in the field of Internet interventions and put forward a number of recommendations that are intended to provide researchers with guidelines when performing clinical trials. First, negative effects are to be acknowledged and examined across treatment conditions as well as between Internet interventions and face-to-face treatment in order to further the understanding of its incidence and facilitate an analysis of causality. Second, a uniform classification of negative effects is proposed to ease monitoring procedures and the process of reporting the results in scientific journals. Third, measuring negative effects should use methods from both quantitative and qualitative research that will be able to detect deterioration as well as the subjective experiences of the patient. Forth, investigating factors associated with negative effects are endorsed as it could delineate underlying mechanisms contributing to its incidence. The recommendations presented in the current paper are in line with the suggestions proposed by Peterson et al. (2013), Linden (2013), and Parker et al. (2013), but extend the discussion of negative effects to the field of Internet interventions, providing practical steps that can guide the research forward and lend valuable information on how to prevent negative effects from occurring in the future.

5. Competing interests

The authors have declared that no competing interests exist.

Acknowledgement

This study was made possible by a generous grant from the Swedish Research Council for Health, Working Life and Welfare (FORTE 2013-1107). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A

1. Is there a problem of negative effects, i.e., can we legitimately speak of a patient getting worse or experiencing adverse events as a result of Internet interventions or related treatments, e.g. smartphone applications?
2. If so, what would constitute a negative effect in Internet interventions?
3. By what criteria would one judge a patient as having experienced negative effects as a result of Internet interventions?
4. While any therapy outcome is obviously a function of many factors, which factors would you associate with, or consider responsible for, a negative effect?
5. In your opinion, is there a difference between face-to-face psychotherapy and Internet interventions in terms of occurrence and nature of negative effects?

References

Andersson, G., Carlbring, P., Grimund, A., 2008. Predicting treatment outcome in internet versus face to face treatment of panic disorder. Comput. Hum. Behav. 24, 1790–1801.

Andersson, G., Paxling, B., Roch-Norlund, P., Ostman, G., Norgren, A., Almlov, J., Georen, L., Breitholtz, E., Dahlin, M., Cuijpers, P., Carlbring, P., Silverberg, F., 2012a. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. Psychother. Psychosom. 81, 344–355.

Andersson, G., Paxling, B., Wiwe, M., Vernmark, K., Felix, C.B., Lundborg, L., Furmark, T., Cuijpers, P., Carlbring, P., 2012b. Therapeutic alliance in guided internet-delivered cognitive behavioural treatment of depression, generalized anxiety disorder and social anxiety disorder. Behav. Res. Ther. 50, 544–550.

Andersson, G., Carlbring, P., Ljótsson, B., Hedman, E., 2013. Guided internet-based CBT for common mental disorders. J. Contemp. Psychother. 43, 223–233.

Andrews, G., Davies, M., Titov, N., 2011. Effectiveness randomized controlled trial of face to face versus Internet cognitive behaviour therapy for social phobia. Aust. N. Z. J. Psychiatry 45, 337–340.

Barlow, D.H., 2010. Negative effects from psychological treatments: a perspective. Am. Psychol. 65, 13–20.

Bergin, A.E., 1966. Some implications of psychotherapy research for therapeutic practice. J. Abnorm. Psychol. 71, 235–246.

Bergman Nordgren, L., Carlbring, P., Linna, E., Andersson, G., 2013. Role of the working alliance on treatment outcome in tailored internet-based cognitive behavioural therapy for anxiety disorders: randomized controlled pilot trial. JMIR Res. Protoc. 2, e4.

Berk, M., Parker, G., 2009. The elephant on the couch: side-effects of psychotherapy. Aust. N. Z. J. Psychiatry 43, 787–794.

Beyerstein, B.L., 2001. Fringe psychotherapies: the public at risk. Sci. Rev. Altern. Med. 5, 70–79.

Boettcher, J., Rozental, A., Andersson, G., Carlbring, P., 2014. Side effects in Internet-based interventions for social anxiety disorder. Internet Interv. 1, e3–e11.

Boisvert, C.M., 2010. Negative treatment effects: is it time for a black box warning? Am. Psychol. 65, 680–681.

Boisvert, C.M., Faust, D., 2002. Iatrogenic symptoms in psychotherapy — a theoretical exploration of the potential impact of labels, language, and belief systems. Am. J. Psychother. 56, 244–259.

Carlbring, P., Andersson, G., 2006. Internet and psychological treatment. How well can they be combined? Comput. Hum. Behav. 22, 545–553.

Carlbring, P., Bohman, S., Brunt, S., Buhrman, M., Westling, B.E., Ekselius, L., Andersson, G., 2006. Remote treatment of panic disorder: a randomized trial of Internet-based cognitive behavior therapy supplemented with telephone calls. Am. J. Psychiatr. 163, 2119–2125.

Castonguay, L.G., Boswell, J.F., Constantino, M.J., Goldfried, M.R., Hill, C.E., 2010. Training implications of harmful effects of psychological treatments. Am. Psychol. 65, 34–49.

Crown, S., 1983. Contraindicators and dangers of psychotherapy. Br. J. Psychiatry 143, 436–441.

Curtin, F., Schulz, P., 2011. Assessing the benefit: risk ratio of a drug—randomized and naturalistic evidence. Dialogues Clin. Neurosci. 13, 183–190.

Danial-Saad, A., Kuflik, T., Tamar Weiss, P.L., Schreuer, N., 2013. Building an ontology for assistive technology using the Delphi method. Disabil. Rehabil. Assist. Technol. 8, 275–286.

Del Re, A.C., Fluckiger, C., Horvath, A.O., Symonds, D., Wampold, B.E., 2012. Therapist effects in the therapeutic alliance-outcome relationship: a restricted-maximum likelihood meta-analysis. Clin. Psychol. Rev. 32, 642–649.

Dever Fitzgerald, T., Hunter, P.V., Hadjistavropoulos, T., Koocher, G.P., 2010. Ethical and legal considerations for internet-based psychotherapy. Cogn. Behav. Ther. 39, 173–187.

Dimidjian, S., Hollon, S.D., 2010. How would we know if psychotherapy were harmful? Am. Psychol. 65, 21–33.

Edwards, I.R., Biriell, C., 1994. Harmonization in pharmacovigilance. Drug Saf. 10, 93–102.

Emmelkamp, P.M., David, D., Beckers, T., Muris, P., Cuijpers, P., Lutz, W., Andersson, G., Araya, R., Banos Rivera, R.M., Barkham, M., Berking, M., Berger, T., Botella, C., Carlbring, P., Colom, F., Essau, C., Hermans, D., Hofmann, S.G., Knappe, S., Ollendick, T.H., Raes, F., Rief, W., Riper, H., Van Der Oord, S., Vervliet, B., 2014. Advancing psychotherapy and evidence-based psychological interventions. Int. J. Methods Psychiatr. Res. 23 (Suppl. 1), 58–91.

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B., 1997. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). American Psychiatric Press, Washington, D.C.

Foa, E.B., Emmelkamp, P.M.G., 1983. Failures in Behavior Therapy. John Wiley & Sons, New York, N.Y.

Foulkes, P., 2010. The therapist as a vital factor in side-effects of psychotherapy. Aust. N. Z. J. Psychiatry 44, 189.

Goldmann, S.A., Kennedy, D.L., Lieberman, R., 1995. In: Food and Drug Administration (Ed.), Clinical therapeutics and the recognition of drug-induced disease (Rockville, MD).

Hadley, S.W., Strupp, H.H., 1976. Contemporary views of negative effects in psychotherapy — integrated account. Arch. Gen. Psychiatry 33, 1291–1302.

Hannan, C., Lambert, M.J., Harmon, C., Nielsen, S.L., Smart, D.W., Shimokawa, K., Sutton, S. W., 2005. A lab test and algorithms for identifying clients at risk for treatment failure. J. Clin. Psychol. 61, 155–163.

Hatfield, D., McCullough, L., Frantz, S.H.B., Krieger, K., 2010. Do we know when our clients get worse? An investigation of therapists' ability to detect negative client change. Clin. Psychol. Psychother. 17, 25–32.

Haynes, S.N., Leisen, M.B., Blaine, D.D., 1997. Design of individualized behavioral treatment programs using functional analytic clinical case models. Psychol. Assess. 9, 334–348.

Heins, M.J., Knoop, H., Prins, J.B., Stulemeijer, M., van der Meer, J.W.M., Bleijenberg, G., 2010. Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome. Psychother. Psychosom. 79, 249–256.

Hoek, W., Schuurmans, J., Koot, H.M., Cuijpers, P., 2012. Effects of Internet-based guided self-help problem-solving therapy for adolescents with depression and anxiety: a randomized controlled trial. PLoS One 7, e43485.

Hofmann, S.G., Suvak, M., 2006. Treatment attrition during group therapy for social phobia. J. Anxiety Disord. 20, 961–972.

Jacobson, N.S., Truax, P., 1991. Clinical-significance — a statistical approach to defining meaningful change in psychotherapy-research. J. Consult. Clin. Psychol. 59, 12–19.

Johansson, R., Bjorklund, M., Hornborg, C., Karlsson, S., Hesser, H., Ljotsson, B., Rousseau, A., Frederick, R.J., Andersson, G., 2013a. Affect-focused psychodynamic psychotherapy for depression and anxiety through the Internet: a randomized controlled trial. PeerJ 1, e102.

Johansson, R., Carlbring, P., Heedman, Å., Paxling, B., Andersson, G., 2013b. Depression, anxiety and their comorbidity in the Swedish general population: point prevalence and the effect on health-related quality of life. PeerJ 1, e98.

Johansson, R., Nyblom, A., Carlbring, P., Cuijpers, P., Andersson, G., 2013c. Choosing between Internet-based psychodynamic versus cognitive behavioral therapy for depression: a pilot preference study. BMC Psychiatry 13, 268.

Johnston, L., Titov, N., Andrews, G., Dear, B.F., Spence, J., 2013. Comorbidity and Internet-delivered transdiagnostic cognitive behavioural therapy for anxiety disorders. Cogn. Behav. Ther. 42, 180–192.

Jorm, A.F., 2012. Mental health literacy empowering the community to take action for better mental health. Am. Psychol. 67, 231–243.

Kalachnik, J.E., 1999. Measuring side effects of psychopharmacologic medication in individuals with mental retardation and developmental disabilities. Ment. Retard. Dev. Disabil. Res. Rev. 5, 348–359.

Kohn, R., Saxena, S., Levav, I., Saraceno, B., 2004. The treatment gap in mental health care. Bull. World Health Organ. 82, 858–866.

Kottler, J.A., Carlson, J., 2003. Bad Therapy: Master Therapists Share Their Worst Failures. Taylor & Francis Books, Inc., New York, N.Y.

Lambert, M., 2007. Presidential address: what we have learned from a decade of research aimed at improving psychotherapy outcome in routine care. Psychother. Res. 17, 1–14.

Lambert, M., Whipple, J.L., Vermeersch, D.A., Smart, D.W., Hawkins, E.J., Nielsen, S.L., Goates, M., 2002. Enhancing psychotherapy outcomes via providing feedback on client progress: a replication. Clin. Psychol. Psychother. 9, 91–103.

Lilienfeld, S.O., 2007. Psychological treatments that cause harm. Perspect. Psychol. Sci. 2, 53–70.

Linden, M., 2013. How to define, find and classify side effects in psychotherapy: from unwanted events to adverse treatment reactions. Clin. Psychol. Psychother. 20, 286–296.

Lindner, P., Andersson, G., Öst, L.G., Carlbring, P., 2013. Validation of the internet-administered Quality of Life Inventory (QOLI) in different psychiatric conditions. Cogn. Behav. Ther. 42, 315–327.

Ljótsson, B., Hedman, E., Andersson, E., Hesser, H., Lindfors, P., Hursti, T., Rydh, S., Ruck, C., Lindefors, N., Andersson, G., 2011. Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial. Am. J. Gastroenterol. 106, 1481–1491.

Mays, D.T., Franks, C.M., 1980. Getting worse – psychotherapy or no treatment – jury should still be out. Prof. Psychol. 11, 78–92.

Mays, D.T., Franks, C.M., 1985. Negative Outcome in Psychotherapy and What to do About It. Springer Publishing Company, Inc., New York.

Mohr, D.C., 1995. Negative outcome in psychotherapy — a critical-review. Clin. Psychol. Sci. Pract. 2, 1–27.

Mohr, D.C., Burns, M.N., Schueller, S.M., Clarke, G., Klinkman, M., 2013. Behavioral intervention technologies: evidence review and recommendations for future research in mental health. Gen. Hosp. Psychiatry 35, 332–338.

Nordgreen, T., Havik, O.E., Ost, L.G., Furmark, T., Carlbring, P., Andersson, G., 2012. Outcome predictors in guided and unguided self-help for social anxiety disorder. Behav. Res. Ther. 50, 13–21.

Nutt, D.J., Sharpe, M., 2008. Uncritical positive regard? Issues in the efficacy and safety of psychotherapy. J. Psychopharmacol. 22, 3–6.
Nyenhuis, N., Golm, D., Kroner-Herwig, B., 2013. A systematic review and meta-analysis on the efficacy of self-help interventions in tinnitus. Cogn. Behav. Ther. 42, 159–169.
Parker, G., Fletcher, K., Berk, M., Paterson, A., 2013. Development of a measure quantifying adverse psychotherapeutic ingredients: the Experiences of Therapy Questionnaire (ETQ). Psychiatry Res. 206, 293–301.
Peterson, A.L., Roache, J.D., Raj, J., Young-McCaughan, S., 2013. The need for expanded monitoring of adverse events in behavioral health clinical trials. Contemp. Clin. Trials 34, 152–154.
Proudfoot, G., Klein, B., Barak, A., Carlbring, P., Cuijpers, P., Lange, A., Ritterband, L., Andersson, G., 2011. Establishing guidelines for executing and reporting Internet intervention research. Cogn. Behav. Ther. 40, 82–97.
Rowe, G., Wright, G., 1999. The Delphi technique as a forecasting tool: issues and analysis. Int. J. Forecast. 15, 353–375.
Seggar, L.B., Lambert, M.J., Hansen, N.B., 2002. Assessing clinical significance: application to the Beck depression inventory. Behav. Ther. 33, 253–269.
Spek, V., Nyklicek, I., Cuijpers, P., Pop, V., 2008. Predictors of outcome of group and internet-based cognitive behavior therapy. J. Affect. Disord. 105, 137–145.
Spinelli, T., 1983. The Delphi decision-making process. J. Psychol. 113, 73–80.
Steketee, G., Shapiro, L.J., 1995. Predicting behavioral treatment outcome for agoraphobia and obsessive–compulsive disorder. Clin. Psychol. Rev. 15, 317–346.
Ström, M., Uckelstam, C.J., Andersson, G., Hassmen, P., Umefjord, G., Carlbring, P., 2013. Internet-delivered therapist-guided physical activity for mild to moderate depression: a randomized controlled trial. PeerJ 1, e178.
Strupp, H.H., Hadley, S.W., 1977. A tripartite model of mental health and therapeutic outcomes. With special reference to negative effects in psychotherapy. Am. Psychol. 32, 187–196.
Strupp, H.H., Hadley, S.W., Gomes-Schwartz, B., 1977. When Things Get Worse: The Problem of Negative Effects in Psychotherapy. Jason Aronson Inc., Washington, D.C.
Stuart, R.B., 1970. Trick or Treatment: How and When Psychotherapy Fails. Research Press, Champaign, I.L.
Titov, N., Andrews, G., Robinson, E., Schwencke, G., Johnston, L., Solley, K., Choi, I., 2009. Clinician-assisted Internet-based treatment is effective for generalized anxiety disorder: randomized controlled trial. Aust. N. Z. J. Psychiatry 43, 905–912.
van Straten, A., Emmelkamp, J., de Wit, J., Lancee, J., Andersson, G., van Someren, E.J., Cuijpers, P., 2013. Guided Internet-delivered cognitive behavioural treatment for insomnia: a randomized trial. Psychol. Med. 1–12.
Wagner, B., Horn, A.B., Maercker, A., 2014. Internet-based versus face-to-face cognitive-behavioral intervention for depression: a randomized controlled non-inferiority trial. J. Affect. Disord. 152, 113–121.
Warmerdam, L., van Straten, A., Twisk, J., Riper, H., Cuijpers, P., 2008. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. J. Med. Internet Res. 10, e44.
Willan, A.R., OBrien, B.J., Cook, D.J., 1997. Benefit-risk ratios in the assessment of the clinical evidence of a new therapy. Control. Clin. Trials 18, 121–130.
Wysowski, D.K., Swartz, L., 2005. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002 — the importance of reporting suspected reactions. Arch. Intern. Med. 165, 1363–1369.