Distress and unmet needs in cancer patients
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Problem-Solving Therapy for distressed cancer patients: problems to be solved in a replica randomized controlled trial.

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Submitted
Abstract

This study reflects on serious methodological problems encountered in a replica RCT, concerning the study of Nezu et al. (2003) on Problem-Solving Therapy (PST) in distressed cancer patients. Although we screened a large sample of patients for distress \( n=970 \), only 3.7\% \( n=36 \) was included in the study and randomized into the PST-intervention \( n=18 \) or waitlist control condition \( \text{WLC}, n=18 \). Moreover, only half of the intervention condition \( n=9 \) received PST as planned, due to inclusion criteria, drop out and adherence problems. We discuss the original study of Nezu et al. and the feasibility of an RCT PST-intervention for distressed cancer patients in the Dutch healthcare context.
5.1 Introduction

The aim of the present paper is to reflect on the methodological problems encountered in a replication of a randomized controlled trial concerning a Problem-Solving Therapy (PST) intervention for distressed cancer patients. Our study intended to replicate the trial of Nezu et al. (1). This RCT incorporated a large sample of distressed cancer patients (n=132) and reported that PST was proven to be strongly effective in reducing distress and depressive symptoms, as well as in improving quality of life of the patients included, with large effect sizes found on distress. The results found in the study confirmed suggestions of several reviews and meta-analyses that a sample of patients with elevated levels of distress is a requirement to find positive effects (2-5). By including also patients with low levels of distress, studies risk an underestimation of possible effects of the intervention due to a floor effect. However, in the years following the start of our replication study, it became apparent that the study of Nezu et al. reported unrealistically high effect sizes for their primary outcome (6-8), and some meta-analyses excluded the study as an extreme outlier (6,7,9).

In two earlier reports, we discussed the difficulties encountered in the recruitment phase of our replication study (10,11). A main finding was that the unmet need for psychosocial services of patients was much lower than expected, even though percentages of patients with elevated distress rates were comparable with other studies (12-14). This low need for psychosocial services in distressed cancer patients has also been observed by others (15,16). A methodological consequence is that the recruitment of distressed patients with an unmet need for services, with the aim to include them in a psychosocial intervention study, requires the assessment of a large sample of patients. We calculated that for our replication study, we should have screened 3240 patients to have reached a sufficiently powered sample (10).

A review study of Moyer et al. summarized recruitment and retention difficulties reported in psychosocial intervention studies in cancer patients, such as a low need for services, disappointment when being randomized to a non-preferred condition, drop out and lack of adherence to treatment (17). A lower than expected recruitment rate and a high drop out of patients are important methodological limitations, being not only a threat for the power of the study or the generalizability of findings (18), but also affecting the already expensive character of an intervention RCT.

Inspired by the review of Moyer et al. and the impression that many intervention studies do not critically reflect on their recruitment process and retention rates (19), we decided to describe and discuss the methodological problems we encountered in our replication trial on PST. In this article, we focus on the differences of our study with the study of Nezu et al., including the differences in cultural and healthcare context, and reflect on inclusion criteria, drop out and protocol adherence. We hope that our article may be of help for researchers planning to conduct comparable (replication) RCTs.
5.2 Method

5.2.1. Participants and procedure
Details of the recruitment process and our measures have been described in detail previously (10). In short, three hospitals in the Netherlands started implementation of screening for distress to recruit cancer patients for the current PST-trial: the University Medical Center Groningen, the Martini Hospital Groningen, and the Radiotherapy Institute Friesland, Leeuwarden. In our replication study, we adopted the design of Nezu et al. on the following important aspects: the use of a sample based on mixed types of cancer, screening for level of distress and elevated level of distress as an inclusion criterion, and randomization over an PST intervention condition and a waiting list control condition.

There were also some differences: a.) Rather than offering the intervention to patients during their treatment trajectory as Nezu et al. did, we offered PST directly after completion of medical treatment. We focused on this period, as research has shown that a considerable proportion of the distress that is manifested at the start of cancer treatment resolves naturally within a few months (20-22); b.) We did not use a convenience sample (selection of patients relying on referral), but a consecutive sample of patients based on routine screening for distress. This choice is consistent with methodological recommendations as well as with current national clinical guidelines (Comprehensive Cancer Centre, the Netherlands) and international clinical guidelines (23), recommending routine screening for distress and referral of distressed patients to psycho-oncological services; and c.) We did not provide financial reimbursement for patients completing the sessions and follow-up measures. In the trial of Nezu et al. patients received 250 dollars after completing all the sessions and follow up measures.

Patients were screened for distress at two points in time: immediately after completion of active medical treatment (T1) and two months later (T2). Eligibility criteria were: 1) a curative cancer diagnosis, 2) ≥18 years of age, 3) ability to understand the Dutch language sufficiently well, 4) a distress score on the Hopkins Symptom Checklist-25 (HSCL-25) ≥39 at T1 or T2, and 5) a self-reported need for psychosocial services. Patients with major communication difficulties, a need for specialist psychiatric care, or already receiving psychosocial care from a psychologist or psychiatrist were excluded. Patients were randomized to either the PST intervention or a waiting list control condition, receiving PST after 10 weeks waiting. The study was approved by the Medical Ethical Committees of the participating hospitals.

5.2.2. PST
Based on the PST protocol ‘Helping Cancer patients Cope’ from Nezu et al. (24), we developed a detailed and structured Dutch PST-manual for therapists with session-to-session descriptions, as well as a workbook for patients, concerning 8-10 weekly
sessions of 45-60 min. on an individual basis. In these sessions the following five components were stepwise addressed: 1) problem orientation, 2) problem definition, 3) generation of alternatives, 4) decision-making, and 5) solution implementation and verification. According to Nezu et al. several therapeutic techniques were prescribed to be used in the sessions, including psycho-education, visualization, coaching, cognitive restructuring, goal-setting, rehearsal, and positive reinforcement.

Seven therapists with at least a master's degree in psychology participated in a three-days PST-training program and conducted the PST sessions for the patients included in the study. Patients had to receive at least 7 out of the 8-10 sessions of the protocol during a maximum of 12 weeks to be eligible as a treatment completer of PST.

5.2.3. Outcome measures

Our RCT intervention study included twelve questionnaires, including measures of distress, quality of life, problem solving ability, coping, and loss processing. As we do not present outcome data, we only focus in this article on the Hopkins Symptom Checklist-25 (HSCL-25) (25) and the Social Problem Solving Inventory-Revised: Short (SPSI-R:S) (26).

Distress
We used the HSCL-25 (25) as screening instrument and outcome measure, and we adopted the lower cutpoint of ≥39 instead of ≥44. With this lower cut point, we gave also moderately distressed patients a chance to participate in the trial. The HSCL-25 is closely related to the Brief Symptom Inventory-18, which is a widely used screening instrument among cancer patients (27-29). The study of Nezu et al. used the larger version of the Brief Symptom Inventory (53 items) and the Hamilton Rating Scale for Depression (HRSD) as screening instruments and outcome measures.

Problem-solving ability
The SPSI-R:S was included to evaluate if decreases in distress would be associated with increases in problem-solving ability. The SPSI-R:S is the shortened version or the 52-item measure of social problem-solving ability (26,30). In addition to a total score, it consists of five scales that measure two constructive dimensions (PPO-Positive Problem Orientation, RPS-Rational Problem-Solving) and three dysfunctional dimensions (NPO-Negative Problem Orientation, ICS-Impulsiveness/Carelessness Style, AS-Avoidance Style). The larger version was used in the study of Nezu et al.

5.3 Results

In total, 970 patients were screened for distress directly after the end of medical treatment, with 423 patients reporting distress, of whom 215 reported a need for services. However, only 52 patients were willing to participate, and 36 patients (3.7% of
970) were found eligible and randomized into the PST intervention (n=18) or the waiting list control condition (n=18). Of the 36 patients participating in the study, the mean age was 55.7 (±8.8), 64% was women, 83% married/living together and 49% highly educated. Patients were diagnosed with breast cancer (19), prostate cancer (6), gastro-intestinal cancer (6), lung cancer (1) and other cancers (4). Median time since diagnosis was 4.8 months (range 1.5-33.7).

Despite structured training of psychologists in the PST-protocol, we found that only half of the patients included in the PST condition (9 out of 18) received the intervention as originally planned (following the protocol ≥7 sessions). The other half of the PST condition (9 out of 18) received the intervention not conform the protocol, for several reasons (Table 1). In the waiting list control condition, 4 patients (out of 18) dropped out because they were disappointed with their group assignment, had transportation difficulties, or could not be contacted by phone or email. The other 14 patients (out of 18) completed the waiting period and started PST. However, only 4 patients followed ≥7 sessions of PST, 5 received PST not as planned, and 5 received no sessions because of a lowered distress score on the HSCL-25 after the waiting list period and no need for services anymore.

**Table 1.** Difficulties encountered in conducting a replication RCT for distressed cancer patients.

<table>
<thead>
<tr>
<th></th>
<th>PST</th>
<th>WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>PST as intended</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td><strong>Ineligible (exclusion criteria)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced distress after a waiting period</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Disease recurrence during PST</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Drop out</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients feeling better after 1-5 sessions</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Disappointment with group assignment</td>
<td>-</td>
<td>2*</td>
</tr>
<tr>
<td>Therapists’ preference for a different type of service</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Therapy being too emotional and confronting</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>No-shows and treatment scheduling problems</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Patients’ dislike of the PST protocol/homework</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other: transportation problems, no contact by phone/email</td>
<td>-</td>
<td>2*</td>
</tr>
</tbody>
</table>

PST= Problem-Solving Therapy; WLC= Waiting List Condition

*These 4 patients did not complete the waiting period.
5.4 Discussion

It is crucial for the power of an RCT and the generalizability of findings to recruit and retain a sufficient number of patients into a trial (18). In practice however, it appears that many psychosocial RCT intervention studies do not reach their planned number of patients to be included in the trial and are therefore limited in their conclusions about the efficacy of their intervention (31-33). In our Dutch replication RCT, we encountered a very high drop out of patients and therefore were unable to present the results of the main outcome measure of our study, namely changes in patients’ level of distress. As conducting an RCT is an expensive and often challenging business, means to improve recruitment and reduce drop out in such trials are very welcome (34,35). Guided by the review of Moyer et al. (17), we use this discussion section to reflect on several methodological aspects of our trial, respectively: methodological decisions, the critical role of inclusion criteria, reasons for drop out and problems concerning adherence to treatment. Thereby, we focus on the differences of the study of Nezu et al. with our study, including the differences in healthcare context.

5.5.1. Methodological decisions and the role of inclusion criteria

In our replication study, we recruited a consecutive sample of patients, which means that we screened all patients routinely, and invited patients with heightened levels of distress to participate. This method is supposed to promote equal access to enrollment in trials and lead to a better representation of the patient population. In contrast, the original study of Nezu et al. included a convenience sample of distressed patients. That is, the authors reported that they included patients from various referral resources who already self-reported significant psychological distress and were interested in participating in the PST trial. In this latter type of sample, the willingness and motivation to participate and retain in a psychosocial intervention is more likely than in a sample only selected by elevated levels of distress. Nezu et al. did not report how many patients were approached to be assessed for eligibility, so we cannot compare these rates with ours. However, of the 150 patients enrolled in the PST trial of Nezu et al., 132 completed the trial and follow-up assessments (88%), which is substantially higher that what we found.

Compared to Nezu et al. we used a slightly lower cut point for distress level as inclusion criterion. Although the choice for this lower cut point promoted our initial recruitment rate, it also may have contributed to our final attrition rate: a substantial number of patients showed a reduction of need for psychological services after a few sessions, or, in the waiting list condition, after the 10-week waiting period. Some psychosocial intervention trials including cancer patients with high levels of depressive symptoms retained more patients in their study compared to studies including distressed patients or studies not selecting patients (1,36,37). On the other hand, higher levels of depression can also be a predictor of drop out in clinical trials, probably
because patients are less optimistic about the outcomes of the intervention (38). Furthermore, a higher level of distress as inclusion criterion may impede recruitment; in one study, recruitment halved when the cut point on the HADS was raised from ≥8 to ≥11 (33). These contrasting findings underline the methodological problem to choose between a moderate distress level as inclusion criterion (e.g. to attain recruitment goals) or a higher distress level (e.g. to assure the need and motivation for receiving the intervention).

5.5.2. Reasons for drop out

The internal validity of a study is threatened when patients drop out because they are disappointed with their treatment condition after being randomized, or when they prefer a different type of services (17,39). In our study, this was the case: some patients were disappointed with being randomized to the waiting list control condition and decided to search for psychosocial services by themselves directly, some disliked the PST treatment protocol and homework assignments and it appeared that the PST protocol did not fit to the complaints of a number of patients (i.e. specific anxiety disorder). In the latter two cases, therapists decided to continue treatment without the PST protocol. The study of Nezu et al. did not report specific reasons of patients to drop out, but they mentioned that patients were strongly encouraged to attend all 10 PST sessions; to ensure patients’ completion of all sessions attempts were made to be flexible in the scheduling of the treatment sessions and assessments. This may have contributed to their high intervention completion rate of rate of 88%.

Compared to other countries such as the USA, in the Netherlands psychosocial services are easily accessible and to some extent financed by the Dutch healthcare system. This easy access to psychosocial services may not only be a reason for patients dropping out, but also one of the main reasons for the low recruitment rate of the present study: it was found that 17%-25% of distressed patients already received psychosocial services during the recruitment phase of our RCT (10,11). This highlights that it is important to take into account the organization of the healthcare system in which an RCT is to be implemented. In a well-functioning healthcare context, where patients already regularly receive a referral or access psychosocial services by themselves, execution of an RCT may result in lower than expected recruitment and retention rates.

In addition, it should be noted that in the study of Nezu et al. and some other psychosocial intervention trials (37), participation was encouraged by financial compensation. This may be a source of participation bias. Especially in countries where psychosocial healthcare is costly, the free access to the trial plus the reimbursement to participate may stimulate participation and positive response tendencies (40). Furthermore, such recruitment strategies will impede insight in how many patients will actually access services when the trial is implemented in normal clinical practice.
5.5.3. Problems concerning adherence to treatment

In our study, the number of PST sessions was relatively fixed in order to replicate the study of Nezu et al. and to guarantee treatment integrity of the trial. However, it appeared that a number of patients in both the intervention and waiting list condition felt they were adequately supported in 1-5 sessions, instead of the 8-10 sessions planned. A qualitative study showed that many cancer patients could be helped by one or two encounters, while others needed more long-lasting support (41). Furthermore, a meta-analysis into the efficacy of PST found that the number of hours of PST treatment was not significantly associated with effect size (8). In some studies in primary care, nurses or physicians delivered PST in 6 short sessions of 30 minutes, which was found to be effective to reduce depressive symptoms (42,43). On the other hand, some of our patients needed additional sessions to feel supported with the problems they encountered; these problems were not always directly related to the illness, but might have been triggered by the cancer experience (41,44).

To improve the adherence problems mentioned above, a flexible treatment protocol with different treatment modalities, and flexibility in the number of sessions and content of the therapy, depending on the type of complaints, may be of help. An example of such a study can be found in an effective trial of Cognitive Behavioral Therapy for cancer survivors to reduce fatigue (45), and a collaborative care intervention for depressed cancer patients (46). Future study designs should investigate whether these more tailored approaches better fit to the needs of patients, and promote retention.

5.5.4. Conclusions and recommendations

The study of Nezu et al. showed promising results of PST on various outcome measures in both short- and long-term. The effect sizes on distress identified were substantially larger than the mean effect sizes that came from an earlier meta-analysis (47), suggesting that PST appeared to be a particularly robust intervention. However, several meta-analyses and systematic reviews concluded that the study of Nezu et al. reported unrealistically high effect sizes for their primary outcome (6-9). After the completion of our replication study, we also raise questions about diverse aspects of the method and results of the study of Nezu et al., i.e. the possibility of selection-bias due to incomplete description of the patient selection process, the potential influence of financial compensation of patients on response-behavior, and the effects on outcomes eventually biased by encouragement to continue participation without attention to the personal needs of patients.

In line with recommendations in literature, we propose that for intervention studies only patients should be recruited with prominent levels of distress (2-5) to be able to offer an intervention that makes sense, but we also strongly advise to pay attention to personal needs of patients with a flexible number of treatment sessions according to the process of the patient.
We concluded that our PST-replication study proved not to be feasible in a Dutch healthcare context. For future psychosocial intervention studies concerning cancer patients, we recommend to take into account several aspects of the cultural and healthcare context in which the RCT is to be implemented. For example: what is the quality and accessibility of medical and psychosocial services, which services are generally and freely available, and how are patients referred to these services? Answers on these questions are necessary for researchers to adjust their trial and inclusion criteria to the remaining unmet psychosocial needs of patients, and to give direction to the discussion with clinical specialists to develop effective trials.

5.5.5. Clinical implications
Clinicians have the task to recognize cancer patients with high levels of distress and refer them to appropriate psychosocial services. To improve the quality of these services, research is needed according to current scientific standards, such as an RCT-intervention design and routine screening for distress. However, the referral of patients to an RCT may be hindered by the fact that it can be unattractive or disappointing for patients, because they will be randomized to a (sometimes non-preferred) treatment condition. At the one hand, routine screening is cost-expensive and provides only small samples eligible for inclusion in RCTs, at the other hand RCTs need to be standardized, which may not fit to the specific needs of a diversity of patients. Therefore, we think there should be more effort to fit the design and content of psychosocial intervention studies, such as RCTs, to the varying needs of patients, being our potential and needed participants in psychosocial intervention studies.

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