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The Therapeutic Alliance in Randomized Controlled Clinical Trials

Key Words
Therapeutic alliance · Doctor-patient relationship · Clinical trials

Summary
The therapeutic alliance, familiar to those who treat patients and conduct clinical trials, is considered by many to be a non-specific effect in research studies. The concept of the therapeutic alliance has its roots in the doctor-patient relationship and has been discussed extensively in the context of psychodynamic psychotherapy. Research has demonstrated that the strength of the alliance is a strong predictor of outcome in psychotherapy and has emphasized its importance in ensuring compliance in pharmacotherapy. However, little empirical research has been conducted which examines the impact of the therapeutic alliance on patient compliance and retention in randomized controlled clinical trials. Moreover, tension and debate exist between those who see the therapeutic alliance as both a necessary and positive component of a clinical trial and those who view it as a confounding variable. Those who view it as a confounding variable argue that this alliance may serve to influence patients' participation and make difficult the assessment of treatment effects.
We report our observations from one study of adults with schizophrenia who were enrolled in a clinical trial of a new antipsychotic medication. We hypothesize that there is an association between the strength of the therapeutic alliance and subsequent compliance and retention of patients enrolled in clinical drug trials. The relationship among these constructs could be tested empirically as could the association between the therapeutic alliance and the assessment of clinical response.

Schlüsselwörter
Therapeutisches Bündnis · Arzt-Patient-Beziehung · Klinische Studien

Zusammenfassung
Das therapeutische Bündnis in randomisiert kontrollierten Studien
Das therapeutische Bündnis, das allen vertraut ist, die Patienten behandeln und klinische Studien durchführen, wird von vielen als ein nichtspezifischer Effekt in Forschungsstudien betrachtet. Das Konzept des therapeutischen Bündnisses hat seine Wurzeln in der Arzt-Patient-Beziehung und wird im Zusammenhang mit der psychodynamischen Psychotherapie intensiv diskutiert. Untersuchungen haben gezeigt, dass die Stärke des therapeutischen Bündnisses ein zuverlässiger Indikator für das Behandlungsergebnis bei Psychotherapien ist und haben auch die Bedeutung dieses Bündnisses für die Compliance des Patienten bei medikamentösen Therapien unterstrichen. Bisher wurden jedoch nur wenige Forschungsarbeiten durchgeführt, welche den Einfluss des therapeutischen Bündnisses auf die Compliance und Retention des Patienten in randomisierten klinischen Studien untersuchen. Ausserdem gibt es Diskussionen und Spannungen zwischen denen, die das therapeutische Bündnis als notwendige und auch positive Komponente ansehen, und denen, die es als eine störende Variable ansehen. Letztere argumentieren, dass dieses Bündnis dazu dienen könnte, die Kooperation des Patienten zu beeinflussen und so den Nachweis der Wirksamkeit einer Behandlung schwierig macht. Wir berichten über unsere Beobachtungen im Rahmen einer Studie mit erwachsenen Schizophrenen, welche mit einem neuen antipsychotischen Medikament behandelt wurden. Wir stellen die Hypothese auf, dass es bei Patienten in klinischen Studien eine Verbindung zwischen der Stärke des therapeutischen Bündnisses und der Compliance und Retention des Patienten gibt. Es wäre möglich, die Zusammenhänge zwischen diesen Annahmen empirisch zu testen, und dies sollte bei der Planung von Studien berücksichtigt werden.

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The Therapeutic Alliance

Shapiro [1] once said that what really matters in psychotherapy and ultimately what determines its success or failure, is not the theoretical orientation or therapeutic modality one uses, but the quality of the relationship the therapist establishes with his or her patients.

A substantial amount of empirical findings exist relating psychotherapy process variables to treatment outcome. One of the most consistent findings in the psychotherapy research literature is that the quality of the relationship between the patient and the therapist is a major determinant of psychotherapeutic effectiveness. The psychotherapeutic literature consistently demonstrates that the success of any therapeutic endeavour depends on the patient and therapist establishing an open, trusting and collaborative relationship or what has been called the therapeutic, working or helping alliance.

The concept of the therapeutic alliance has long-standing roots in the doctor-patient relationship and has been discussed extensively in the context of psychodynamic psychotherapy. Prior research has demonstrated that the failure of patient and therapist to form an alliance is strongly associated with some of the following factors:

1) an increased dropout rate in both psychotherapy and pharmacotherapy,
2) non-compliance with treatment plans and goals,
3) premature treatment termination,
4) poor treatment outcome.

Researchers have proposed various definitions of the therapeutic alliance. Krupnick et al. [2] defined the therapeutic alliance as the collaborative bond between therapist and patient. Similarly, Foreman and Mamar [3] defined the therapeutic alliance as the ability of therapist and patient to work together in a realistic, collaborative relationship based upon mutual respect, trust and commitment to the work of treatment.

Bordin [4] formulated a tripartite model of the therapeutic alliance in which he suggests that there are three alliance components: (a) the bond between patient and therapist, (b) agreement on goals, and (c) agreement on tasks. Bordin's model contains both a relational component which stresses the importance of the affective aspects of the alliance, and a cognitive component which focuses on an agreement between the patient's and therapist's in terms of the various tasks and goals of treatment.

Bordin [4] and Wolfe [5] both point to the therapeutic alliance as a very important variable, meriting further investigation that is believed to influence outcome across a wide variety of psychotherapies, regardless of their therapeutic and methodological differences.

Although a good deal of literature exists which focuses on the relationship between the therapeutic alliance and treatment outcome, particularly in the area of psychotherapy, little empirical research has been conducted examining the role of the therapeutic alliance specifically in the area of patient compliance and retention in randomized controlled clinical trials. Furthermore, tension and debate exist between those clinicians who view the therapeutic alliance as both a necessary and positive component of a clinical trial and those who view it as a confounding non-specific factor. Recently however, a number of investigators have started to examine the role which the therapeutic alliance plays in clinical drug trials and in turn recognize its importance.

Therapeutic Alliance and Pharmacotherapy

Krupnick and colleagues [2] reported on an empirical investigation of the relationship between the therapeutic alliance and outcome in both psychotherapy and pharmacotherapy. One of their most interesting findings was the strong association between alliance and outcome in pharmacotherapy, under both active and placebo conditions. This finding suggests that the therapeutic alliance may strongly influence both active and placebo response, acting as a factor above and beyond the specific pharmacologic action of the drug alone. The therapeutic alliance may somehow create a 'holding' environment enabling compliance to be enhanced as well as allowing issues and concerns to be addressed and worked through within the context of a supportive and collaborative relationship, e. g., concerns such as dependence on medication and problematic side effects. In pharmacotherapy, a positive doctor-patient relationship has been viewed as an important factor in compliance, although active medication is still considered to be the primary agent of change. It has been suggested however, that certain non-specific factors which are quite distinct from pharmacological properties might coexist synergistically with medication effects. Researchers have demonstrated that in the clinical evaluation of psychopharmacologic agents, there are many variables which operate simultaneously with the pharmacological effects and which may independently have an effect on the patient's symptomatology, e. g., variables such as clinic environment or consistent interaction with study staff.

According to Hankoff et al. [6] progress in psychopharmacological treatment has taken place in a frame of reference largely detached from that of the interpersonal sphere seen in psychiatry. Impressive advances in new psychiatric medications have encouraged an orientation to the problem in terms of the classic double-blind, placebo-controlled clinical drug trial which is considered to be the gold standard and represented a major step forward in clinical research. Clinical trials as presently designed often isolate and standardize rather than link the various components of treatment. With increasing experience including our own, it has become apparent that psychopharmacological treatment contains all of the complexities that any treatment in psychiatry contains. Along with the 'pure' pharmacological effects of a drug, there are numerous non-pharmacological factors that are at work in treatment. Sheard [7] found that certain non-specific factors might possibly play a role in a patient's decision whether or not to remain in treatment, whether it be psychotherapy or, as we have observed, in our clinical trial.

Hankoff et al. [6] studied the doctor-patient relationship in 30 schizophrenic out-patients receiving combined drug and brief psychotherapy. He found that it was not the doctor's or patient's attitude

alone, but the combination of an effective medication with a strong therapeutic alliance that was significant for the clinical outcome. Psychotherapy and medication have the potential for substantial synergism in the treatment of psychiatric disorders. Effective medications with few or minimal side effects may help achieve an affective climate in which the patient is better able to utilize treatment. With the advent of the newer atypical neuroleptics such as Clozapine, Risperidone and Olanzapine, many patients have reported increased compliance due to a reduction in the amount and severity of problematic side effects that previously would have contributed to non-compliance. In our clinical trial, once the active medication had reached therapeutic levels, subjects as well as clinicians witnessed a decrease in psychotic symptoms. This resulted in an enhancement of their cognitive function and ability to process information. They reported an improvement in their interpersonal skills which resulted in an increased ability to form a therapeutic alliance. Schizophrenic patients given medication which effectively improves their clinical condition by suppressing the delusions, hallucinations and paranoid thinking are in turn less anxious and preoccupied. This results in an increased ability to concentrate and actively and collaboratively participate in treatment, allowing patients to lead better and more productive lives. Any good match between the patient, the clinician and the medication enables this process to take place.

Hankoff et al. [6] found that the consistency of this relationship was seen as a highly favorable condition for continuation of treatment. Consistency here refers to a continuous, predictable and stable relationship with the same clinicians over an extended period of time. Study patients were seen on a regular basis by the same psychiatrist, research assistant and clinic staff throughout the duration of the study. Appointments were scheduled at a set time each week, giving participants a sense of continuity, and stability. We postulated that this consistency was important for our study patients in the following ways:

1) The consistency gave subjects a sense that a knowledgeable, trustworthy and dependable clinician would be there at a set time each week; someone that they could come to know and trust during the course of the study.
2) The study staff might serve as an external locus of control motivating our study patients to comply with medication and treatment recommendations.

We found that when a consistent relationship is combined with an effective medication, this leads to a long-term positive clinical outcome.

From our experience, we hypothesize that a dynamic similar to that of the therapeutic alliance seen within psychotherapy is present during the course of a clinical drug trial. We report our observations from one study of adults with schizophrenia who were enrolled in a clinical trial of a new antipsychotic medication. This dynamic might contribute to a decreased dropout rate during the course of the clinical trial as well as an increased rate of compliance. We postulate that there is an association between the strength of the alliance and subsequent continued compliance and retention of subjects enrolled in clinical drug trials. The relationship among these constructs could be tested empirically as could the association between the therapeutic alliance and the assessment of clinical response.

Understanding the role of the therapeutic alliance in clinical trials of pharmacologic agents poses a particular challenge, and it is perhaps natural that some researchers in the field of psychopharmacology have chosen to focus on other areas apart from the interpersonal ones. The concept of the therapeutic alliance as having a role in clinical drug trials is not something that all researchers are comfortable with. In contrast to psychotherapy where the therapeutic alliance is of prime importance in terms of treatment outcome, in psychopharmacology research especially that of clinical trials, this same relationship is not normally seen as crucial to outcome.

For the past few years, the Payne Whitney Clinic has been part of a multi-center double-blind clinical trial comparing a new psychiatric medication to a conventional antipsychotic in the treatment of patients with schizophrenia. It is important to note that there was no placebo arm as part of the study design and all subjects enrolled in the trial received active medication.

Although we did not start out with the goal of studying the therapeutic alliance, as the clinical trial progressed we began to observe the following: while some subjects dropped out, others were able to remain in the study until the study was completed. We therefore started to think about those factors which might differentiate dropouts from continuers. We hypothesized that those subjects who did not drop out seemed to be able to form a strong therapeutic alliance as compared to those who dropped out during the course of the trial. A relationship seemed to exist between the strength of the alliance and an increased level of subject retention and compliance. Since we did not seek to examine the therapeutic alliance empirically from the study's inception, we did not have any clinical measures to assess the strength of this alliance. Subjects were assessed using structured and semi-structured questionnaires chosen by the sponsor of the study.

Mohl et al. [8] investigated whether something analogous to the therapeutic alliance develops or fails to develop in the initial screening interview and whether this might correlate with retention in psychotherapy. Mohl's hypothesis was that those patients who did not experience a developing therapeutic alliance in the initial or screening interview would be more likely to drop out of therapy early. Mohl's results tended to confirm his hypothesis that interactive effects between screener and patient can influence the likelihood of patients dropping out. Early dropouts experienced a less positive helping alliance than did the continuers. Patients who viewed clinicians as knowledgeable, professional, empathetic and respectful were less likely to drop out earlier. We wondered if Mohl's hypothesis would hold true for our subjects.

In our clinical trial, not all of the subjects chose to remain in the study to its conclusion. Out of the total number of subjects that were initially enrolled, those who dropped out did so early on in the study; within the first 6 weeks of their enrollment. Frank and Gundersen [9] suggested that the most critical period for strengthening the therapeutic alliance is in the beginning stages. In examining some of the key factors which may have contributed to

subjects dropping out we speculated that either they were unable to form a therapeutic alliance or enough time had not elapsed for the alliance to form, by the time these subjects dropped out. Another possibility was that the group of subjects who dropped out did so due to the severity of their psychopathology as well as the ineffectiveness of the medication to alleviate their particular symptomatology.

The Consistency Factor

As clinical researchers, we agree with Hankoff et al. [6] that the consistency of the therapeutic alliance has been shown to be a highly favorable condition for the continuation of treatment. The alliance needs to be based on a sense of honesty, trust, validation and respect. The patient as well as clinician needs to agree that working together collaboratively towards a common treatment goal is crucial. We spoke with each of our subjects individually and asked them to try and pinpoint some of the reasons for their continued participation in the study. Many of them responded by saying that the staff treated them with respect, validated their symptoms as well as their reality and offered them a sense of hope for both the present and the future. Our willingness to spend time with each individual subject discussing what might happen during the course of the study and in turn allowing each subject to have some level of control over their treatment was an important factor in terms of their continued participation. Hope is not empirically quantifiable but is ever-present in treatment. It is one of the nonspecific factors that seems to contribute to patient improvement. According to Byrne et al. [10] hope is the anticipation of a future which is good and based upon: a) shared relationships with others (b) a sense of personal competence (c) an increased coping ability, psychological well-being, purpose and meaning in life, as well as a sense of 'the possible'. The anticipation may or may not be founded on concrete real-world evidence. In schizophrenia relationships with others, a sense of personal competence, coping abilities and psychological well-being are often compromised by the illness itself and the fact that a medication may exist that offers the patient with schizophrenia the possibility of being able to regain some of those capacities in itself may foster a sense of hope and in turn contribute to the formation of a strong therapeutic alliance. One of our subjects pointed out that a key factor contributing to her continued participation was the fact that we advocated on her behalf and held out hope and confidence for her future professional goals. This in turn led to a positive clinical outcome as well as to the fact that she remained in the study until its completion.

According to Beitman and Klerman [11] the stages involved in the formation of a therapeutic alliance can be described as: (1) engaging the patient, (2) establishing trust, and (3) negotiating a treatment plan. In order to accomplish this, the clinician needs to be empathic to the patient's feelings and concerns and communicate that as a knowledgeable clinician, their problems are understandable and potentially solvable. In addition, considerable flexibility is needed in establishing each patient's alliance, on some level giving it a custom-made quality. In a study on lithium compliance Cochrane and Gitlin [12] found that the physician's attitude had an important effect on compliance: *'if the patient reports that his or her psychiatrist believes in the medication, and if the patient is motivated to comply with treatment, then the patient will have a more positive attitude toward the treatment, will report more intention to comply with the regimen and will in fact report greater compliance with treatment'* [12, p. 457].

Parameters of the Alliance

As clinicians we found that by tailoring the therapeutic alliance to each individual subject, collaboration can be enhanced greatly. How the clinician tailors the alliance depends upon the patient's diagnosis, degree of impairment and personality style. An awareness of these factors can be useful in the understanding and interpretation of patterns of compliance and non-compliance. For example, dependent patients can be the physician's most compliant patients as they want to be liked and accepted by their clinician. Because of their particular personality style, these patients may either take the medication to please the physician or report taking it when in fact they are not; rather than risk the possibility of being rejected by the physician for complaining. One of our subjects, a 47–year-old male entered the study with a history of chronic paranoid schizophrenia. The patient was able to establish a strong therapeutic relationship with the study staff over time, periodically reporting that he had missed a dose of medication. He was able to tell the staff when he was experiencing persecutory delusions which consisted of voices in his head accusing him of shoplifting. We found that it was crucial to consider this patient's particular personality style when seeking to establish a strong therapeutic alliance.

Two other study subjects, both of whom had compulsive and paranoid personality styles subsequently had different needs and we had to adjust the parameters of the alliance accordingly in order for them to remain compliant. These particular subjects required reassurance as well as extensive explanations regarding their treatment. They needed to know that as subjects, they had some control over their treatment. In tailoring the therapeutic alliance to each individual subject, the clinician must decide how to balance independence with authority. One of our goals had been to assist subjects in becoming more independent and less reliant on the study staff, while at the same time evaluating their degree of impairment in order to plan a strategy which addressed issues of compliance with the medication; while also guarding against relapse and dropping out. With more impaired subjects, the alliance might need to be stronger than with less impaired subjects who are capable of more autonomy and are willing to utilize it. The clinician must also decide upon the degree of warmth and intimacy the subject can tolerate. For example, while histrionic and dependent patients respond to warmth, schizophrenic patients tend to distrust it. The experience which we had with our subjects tended to differ. Our

study patients, who all carried a diagnosis of chronic paranoid schizophrenia, responded well to warmth and caring. When I asked them personally what contributed to their remaining compliant, they all echoed the fact that warmth, caring and encouragement by the study personnel were important factors for them. They appreciated the fact that they were given respect and not treated as 'guinea pigs'. They also felt that the staff genuinely cared about them and were responsive to their needs. When one of our subjects talked about her fear of gaining weight as a problematic side effect of the medication, we did not tell her that she would need to tolerate the weight gain as a small price to pay for feeling better. We sought instead to validate her concerns about the weight gain and tried to offer her some doable, concrete suggestions to address her concerns. We sat down together and talked about ways to lose weight by eating better nutritionally and starting to do some exercise. We tried to include her in the process as much as possible rather than telling her what we thought was best. When another subject complained about feeling overly sedated, we worked together to change the dose time in order to see if that would be helpful. We felt that effective communication between clinician and subject would be a key factor in retention.

According to Beitman and Klerman [11], a good treatment plan should also include the sequence of recovery. Talking to our subjects individually about what they might expect during the course of the study helped them to know what to anticipate both in terms of their treatment and recovery. When giving instructions to subjects, the clinician needs to use language and terminology that they can understand yet at the same time not make it seem like the clinician is talking down to the subjects. For subjects who have difficulty understanding things, concrete and readable instructions are in order. With respect to information concerning side effects subjects may not know what questions to ask or may be afraid to broach the subject for fear of being perceived as a bother. Therefore, keeping an open line of communication between subject and clinician is crucial since subjects who drop out may do so because of side effects. Almost all our study patients had previously been on multiple medications and tended to stop taking their medication due to problematic side effects that interfered with their daily functioning. Some had developed a mistrust of psychiatric medications and although they expressed a sense of excitement about taking an new medication that might offer them some modicum of relief, they were also skeptical of the new medication not working or giving them problematic side effects. Furthermore, we sought to validate their previous negative experiences with medication yet at the same time encouraging them to try something new; to trust us, our knowledge and our judgement. Knowledge about one's treatment ultimately leads to a sense of power and control over one's symptoms and illness. Medication noncompliance is a major problem in drug treatment as well as in clinical trials. Examples of noncompliance can vary between taking too much medication to alternating irregularly between taking too much or too little. While studies have explored numerous ways to assess and increase medication compliance, we found the single best way to inquire about compliance was in an open, nonjudgmental manner. We were able to objectively assess medication compliance by weekly blood tests that measured the amount of medication in each subject's bloodstream. Subjects can also be asked: 1) how often they missed taking their medication 2) if the medication is not working yet and 3) if they have decided to stop the medication entirely and why. Another important factor that undoubtedly contributes to noncompliance is adverse side effects. In our study, weight gain and sedation were the most prevalent and problematic side effects. When issues such as these arose, we would often spend time trying to come up with a plan so that the subjects would remain compliant. By assuring subjects that their input was just as important as ours, they seemed to feel that they had some control over their treatment. Providing subjects with honest and straightforward information about possible medication side effects engages them in their own treatment without increasing the likelihood of medication noncompliance.

Medication compliance can be enhanced considerably if a good, communicative, trusting relationship exists with a clinician who is caring, strong and positive. A better outcome may be achieved by spending time with the patient, expressing concern and interest in the patient's welfare and demonstrating a confident, professional manner. The physician should convey both a realistic and optimistic attitude about the treatment without creating false hopes. Patients who develop an unrealistic hope eventually may feel worse because of disappointment.

Flexibility of the Relationship

As patients improve and gain more autonomy, the clinician must be prepared to allow them a wider range of choices and decisions. For example, one of our subjects, a 34-year-old female with a diagnosis of chronic paranoid schizophrenia had the opportunity to relocate temporarily in order to enroll in a one-year course to help her prepare for her professional exams. After some discussion among the team as well as with the patient, all parties felt that given her improved condition it would be advantageous to allow her to relocate temporarily and fly back to New York for her monthly visits. The study team realized that by allowing her more autonomy and not discouraging her from moving, the team had reinforced their sense of confidence in her abilities and instilled in her a sense of hope for the future, with the end results being positive. Presently, she is doing extremely well in her profession.

A 38-year-old single woman with a diagnosis of chronic paranoid schizophrenia remained with us for the duration of the study. Prior to entering the study, she had numerous psychiatric hospitalizations. Upon her discharge from the hospital in 1994 she entered the study and went to live in a supportive housing community with her infant son. Eventually, her clinical condition improved to a point where she and her son were able to move into their own apartment in her family's house. When this subject entered the study, she was paranoid and distrustful but was soon able to relate to the study staff in such a way as to begin to form a strong therapeutic alliance. She recently enrolled her son in a Head Start Program and has started to think about returning to work. She is more goal-

directed and focused and felt that the study personnel showed her a consistent sense of caring, concern and respect. This consistency was one of the major factors that contributed to her compliance with the medication and treatment. Currently, this particular subject is being followed in our clinic and her psychiatrist reports that she is doing well and has been compliant with her medication. He also added that she has been able to establish a positive therapeutic alliance with her current therapist as well. We had the opportunity recently to meet this patient in our outpatient clinic and are happy to report that she and her son are doing very well. She told us that she is planning to enroll in a job training program with her eventual goal being to return to work.

Frank and Gundersen [9] suggest that the most critical period for strengthening the therapeutic alliance is between the third and sixth months of therapy. In their analysis of outcome, they observed that patients who had strong therapeutic alliances were functioning better both in terms of symptomatology and psychological well-being. Patients were also more likely to be compliant with medication. Emphasis also should be placed on the importance of the therapeutic alliance, both in supporting the patient through life events and in promoting ongoing medication compliance. Although the authors are the first to acknowledge that their study could not determine whether a strong therapeutic alliance promoted a better outcome or was instead a consequence of improvement in symptoms (perhaps due to better medication compliance and fewer medication side effects) this study is particularly important in that it lends credence to the positive value of a confiding psychotherapeutic relationship for patients with schizophrenia.

The practice of psychiatry requires that the psychiatrist listen attentively and respectfully in a nonjudgmental manner to all communication; even the idiosyncratic or irrational. Many of our subjects have previously experienced disbelief and criticism and for some their alienation is acute. They need acceptance and understanding from the clinician, not disagreement or disbelief.

The practice of medicine is founded on a bond of trust between patient and doctor and we expect the clinician to work actively and with sensitivity and respect to encourage a trusting and respectful relationship, providing the first building blocks in developing the therapeutic alliance.

Conclusion

In conclusion, the therapeutic alliance is a powerful enhancer of patient retention and compliance with treatment regimen. We agree with Downing and Rickels [13] that it would be important to take nonspecific factors such as the therapeutic alliance into consideration in order to optimize the efficiency, accuracy and precision of clinical drug trials. We recommend that investigators design formal studies where the therapeutic alliance can be empirically measured as it relates to treatment outcome. If it can be shown that a strong and positive therapeutic alliance only serves to enhance patient compliance and decrease dropout rates, then we might want to think about integrating this concept into future clinical trial designs. Instead of viewing the therapeutic alliance as a confounding variable or factor, we might instead want to see it as a contributory one, working alongside an effective medication. The extent of its contribution must be measurable so as not to compound data analysis in multi-site studies, ultimately realizing that the therapeutic alliance is a key factor in treatment outcome and should not be discounted in both clinical care and subsequent data analysis.

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