

**EDUCATION, INITIATIVES, AND
INFORMATION RESOURCES**

**One Size Does Not Fit All: Aptitude \times Treatment
Interaction (ATI) as a Conceptual Framework for
Complementary and Alternative Medicine Outcome Research.
Part 1—What Is ATI Research?**

OPHER CASPI, M.D., Ph.D., and IRIS R. BELL, M.D., Ph.D.

ABSTRACT

When multiple treatment choices are available, the question is not just “which treatment is the best?” but more importantly “best or better for whom, when, and why?” Aptitude (or attribute) by treatment interaction (ATI) is a research paradigm that attempts to examine exactly that—how outcome depends on the match or mismatch between patients’ specific characteristics and the treatment they receive. The purpose of this two-part paper is to introduce ATI methods as a conceptual framework into complementary and alternative medicine/integrative medicine (CAM/IM) outcome research. Part 1 presents key concepts in ATI research. Part 2 will present ATI research designs and discusses their applications to the examination of the relationships between individuals and therapies, and the illumination of the mechanisms that make therapies differentially effective. Based on this examination, we conclude that ATI research offers invaluable insights into the multifaceted package of care typically delivered in contemporary medicine and therefore should be included in the portfolio of all CAM/IM outcome research.

INTRODUCTION

Increasingly, medical treatments are administered as part of multifaceted packages of care that contain a variety of therapeutic components. However, such an approach to patient care may inadvertently present some unique challenges. First, from the patients’ cognitive standpoint, research suggests that medical care that involves multiple alternative therapeutic options may result in paradoxical paralysis (Redelmeier and Shafir, 1995). Second, from a practical standpoint, it is unclear whether complex packages of care, compared to more limited approaches, result in better outcomes (National Center for Complementary and Alternative Medicine, 2000). Last, from a health policy standpoint, it is questionable whether this multifaceted approach to patient care is effective, efficient, and economically justifiable at a time of “growing complexity of health care, which today is char-

acterized by more to know, more to do, more to manage, more to watch, and more people involved than ever before” (Institute of Medicine, 2001).

However, offering complex multifaceted packages of care is challenging in at least one other way. It results in more difficulty in making causal inferences regarding the relationship between intervention(s) and outcome(s). This is because, depending on the situation, it is possible that some components of the package of care may augment each other, others may be redundant of each other, and still others may cancel out each other’s effects (Shoam and Rohrbaugh, 1995). Add to this the fact that human beings are uniquely complex and the result is a difficult puzzle to solve. Therefore, outcome research that fails to account for this complexity systematically may inadvertently reach a misleading conclusion. For example, null findings from comparative outcome studies may obscure systematic individual differ-

ences in response to specific treatments, and differentially effective treatment may be the result of systematic, predictable differences at the patient level (Shoam and Rohrbaugh, 1995). Hence, for outcome research the key question is not just, “which treatment is the best?” but more importantly “best or better for whom, when, and why?” (Snow, 1991).

Aptitude (or attribute) by treatment interaction (ATI) is a research paradigm that attempts to examine exactly that—how outcome depends on the match or mismatch between patients’ specific characteristics and the treatment they receive. It promises to examine the relationship between individuals and therapies with respect to outcome and to illuminate the mechanisms and processes that make therapies differentially effective (Cronbach, 1957; Shoam-Salomon, 1991). However, despite its pragmatic, heuristic, and methodological appeals (to come in Part II) ATI research has been used only sparsely in decades of research in diverse fields such as education, psychology, and medicine (Beutler, 1991; Dance and Neufeld, 1988; Shoam-Salomon, 1991; Shoam-Salomon and Hannah, 1991; Smith and Sechrest, 1991; Snow, 1991). Thus, its promise remains largely unfulfilled, perhaps in part due to lack of awareness.

The purpose of this two-part paper, therefore, is to introduce this cluster of ATI research design and analysis methods as a conceptual framework into the growing portfolio of outcome research. Because the principles and theory of ATI research are generic and *de facto* pertain to all avenues of human therapy, our hope is that the papers will stimulate more hypothesis-driven outcome research across all medical disciplines and specialties.

WHAT IS ATI RESEARCH?

In a series of publications in the mid 1950s Edwards and Cronbach (1952) and later Cronbach (1957) proposed an innovative way to relate individuals to outcomes. Rather than looking for main effects, they suggested looking at the “[o]therwise neglected interactions between organismic and treatment variables” (Cronbach, 1957) so as to discover “[s]pecific types of persons and situations for which [treatment] is superior” (Edwards and Cronbach, 1952). They termed this new approach to outcome research Aptitude–Treatment Interaction (ATI).

ATI research is designed to systematically take into account individual differences in the process of treatment evaluation. It is meant to assess the degree to which different treatments have different effects as a function of persons’ characteristics so as to examine whether particular treatments can be chosen or adapted to optimally fit a particular person (Snow, 1991). As such, rather than asking, “who benefits most from (undifferentiated) therapy?” or “what therapy is best for (undifferentiated) patients?,” ATI research focuses on the question, “what kind of therapy, or elements

thereof, benefits what kind of patient?” (Shoam-Salomon and Hannah, 1991).

In the ATI paradigm, the “A” (aptitude or attribute) stands for any individual difference variables or patient characteristics that may moderate the effects of a treatment (T) on an outcome (O). The “T” may represent any type of intervention, from a whole (“integrated”) therapy package to a specific, even single intervention. As explained below, it refers not only to the intervention itself, but also to characteristics of the environment in which the therapy takes place, and the therapists’ characteristics. The “I” (interaction) term is used in a statistical (not social) sense, referring to the moderating effect of A on the relationship between T and O (Shoam and Rohrbaugh, 1995).

To illustrate what ATI research is about better, consider the relationship between “absorption” and treatment as an example. The personality trait of absorption reflects an individual’s capacity to immerse oneself in a self-absorbing experience. Neff et al. (1983) reported that how patients respond to treatment for headache could be predicted by their level of absorption. That is, patients with vascular headaches high in absorption responded well to relaxation training but not to biofeedback while low absorbers improved significantly after biofeedback training. On the other hand, patients with tension headaches high in absorption responded better to biofeedback while those low in absorption did not respond significantly to either biofeedback or relaxation. Likewise, earlier research had shown that high absorbers did better with internal imagery methods while low absorbers did better with external biofeedback methods (Qualls and Sheehan, 1979, 1981). Shea (1985) found that males low in absorption achieved better voluntary control of heart rate with hypnosis compared to imagery. Gregerson et al. (1996) observed that high absorbers increased mucosal immunoglobulin A (IgA) in saliva using a combination of relaxation and imagery, whereas low absorbers decreased mucosal IgA under the same intervention. Taken together, these studies suggest that prior knowledge of patient characteristics may be useful for tailoring the kind of intervention that would be most effective.

In what follows we describe ATI research in more details. The rest of this paper explicates what exactly is meant by “aptitude,” “treatment” and “interaction”. Part 2 will present ATI research designs and discuss their applications with respect to the examination of the relationships between individuals and therapies, and the illumination of the mechanisms and processes that make therapies differentially effective.

APTITUDE

The term aptitude as used within the ATI framework refers to a complex set of personal characteristics identified before and during treatment that are hypothesized to be causally related to the person’s outcome at the end of the

treatment. According to Snow (1991), aptitudes can be related to all relevant individual differences, whether cultural, psychologic, or biologic. It is not limited to intelligence or some fixed list of differential abilities. Nor is any particular personality theory implied. Rather, aptitude refers to a heterogeneous set of personality and motivational variables along with styles, attitudes, and beliefs, to name only a few of the constructs and variables that are of interest in this research paradigm. Some researchers (Shoam-Salomon and Hannah, 1991) have even advocated that aptitude be expanded to include relational variables (e.g., the quality of the patient's marriage; Barlow et al., 1984; Rohrbaugh et al., 2002). An aptitude is thus a dynamic, relational, and contextual construct.

Increasingly, aptitudes are being treated not just as dynamic constructs, but more as processes that, once activated, can affect the treatment that has activated them (Snow, 1980). This reciprocal relationship may alter the course of treatment, the meaning attributed to it, and the aptitude processes involved reflecting aptitude as a state not just a trait (Shoam-Salomon and Hannah, 1991; Snow, 1991). Review of the ATI literature reveals, however, that most ATI research focuses on presumably stable patient characteristics such as personality traits and coping styles (see Dance and Neufeld, 1988, for a review). Again, this seems to be an unwarranted simplification because it assumes that the stable patient characteristic, measured before therapy, interacts with the treatment to influence treatment outcome (Shoam and Rhorbaugh, 1995). Looking at aptitude as a process rather than as a fixed entity implies that the treatment may produce a change in the moderator variable itself. Thus, moderators, when shaped by the treatment, may turn into mediators and further interact with the treatment (Shoam and Rohrbaugh, 1995). For example, patients' expectations were shown to moderate and mediate various medical outcomes such as quality of life (Carr et al., 2001; Crow et al., 1999).

Many researchers have advocated examining process variables that may as well moderate the effects of a treatment (Mitchell and Cormack, 1998; Shoam and Rohrbaugh, 1995; Snow, 1991). Di Blasi et al. (2001), for example, examined whether doctor-patient relationships have an important therapeutic effect, irrespective of any prescribed drug or treatment. Their findings that some physicians' styles are more effective than others (for example, adopting a warm, friendly, and reassuring manner) suggest that if we really are committed to understanding outcomes research, we need to consider provider aptitudes in addition to patient aptitudes. Indeed, the recent JNC 7 report on prevention, detection, evaluation, and treatment of hypertension suggests that empathy and trust may mediate patients' outcome through their effect on adherence to treatment (Chobanian et al., 2003).

TREATMENT

Within the ATI framework, it is imperative to define what exactly is meant by "treatment". Only labeling a treatment

one way or another is not enough. Consider individualized psychotherapy as an example. No two sessions are alike. So just labeling treatment as "psychotherapy" may represent only a remote approximation for the infinite richness of the therapeutic experience. Labels, in short, do not make treatments what they are. That is, patients interact with the treatment as it is administered and not with its label or theoretical orientation (Shoam-Salomon and Hannah, 1991).

Rohrbaugh et al. (2002), advocated a dismantling approach to packages of care. According to their method, studying isolated treatments, or treatments within treatments (little ts, in their language) instead of "integrative, broadband, multi-component treatment packages" (big Ts, in their language) will allow us to understand better which aspect(s) of the integrative package make a difference for whom, or how the various components (alone or in combination) actually work. However, this approach does not take into consideration the possibility that the whole may exhibit properties that its separate parts do not possess. Thus, unlike the reductionistic approach to research that typically examines singular parts of health care and parts of the individual, one at a time, but not the complete system, we advocate for a more integrative approach that studies the whole (Bell et al., 2002). And yet, adopting the latter approach poses some real challenges. For example, if ATIs are real, should we expect certain patient characteristics to interact with the whole treatment package itself (as if it were a single independent variable) or with a specific element of that intervention? If so, which one: the "specific," the "nonspecific," or perhaps both? (Caspi and Bootzin, 2002; Grünbaum, 1985).

ATI research seems particularly useful within the framework of this debate. It can help determine whether interaction exists between little ts and big Ts, such that the effectiveness of a specific intervention depends on the larger model in which it is applied (a phenomenon known as "contextual moderation"; Shoam and Rhorbaugh, 1996). Evidence of such interaction casts doubt on the empirical legitimacy of decontextualizing specific intervention techniques (little ts) by using them in other (big Ts) context. Elsewhere, we have argued that the "cut-and-paste" approach toward complementary and alternative medicine integration, in which empirically supported therapies are integrated into the health care delivery system without considering their philosophical underpinnings, is too reductionistic (Bell et al., 2002; Caspi, 2001). ATI research allows us to test this proposition.

OUTCOMES

Choosing the "right" outcome(s) seems to be an especially challenging task in the ATI research paradigm. This is because different individuals may experience qualitatively different but equally worthwhile outcomes as a result of receiving the same therapy (Shoam-Salomon and Hannah, 1991). For example, Shoam-Salomon et al. (1989) hypoth-

esized and found that given paradoxical interventions (i.e., trying to induce change by discouraging it), high-reactance clients manifest a behavioral change, whereas low-reactance clients manifest a cognitive change. The former have become more effective in their daily behaviors, whereas the latter have derived improved self-efficacy for dealing with their problems.

The realization that different individuals may experience qualitatively different but equally worthwhile outcomes led Shoam-Salomon and Hannah (1991) to propose aptitude-outcome interaction (AOI) as another type of interaction worth studying. However, despite the fact that both ATI and AOI can shed light on the processes of therapeutic change, they are distinctly different. In ATI research one studies the differential effectiveness of at least two therapies for individuals who vary on at least one relevant aptitude. The outcome criterion is common to both therapies. In AOI, on the other hand, one focuses on one therapy and at least one aptitude but seeks an interaction that is manifested in different outcome criteria (Shoam-Salomon & Hannah, 1991). Smith and Sechrest (1991) proposed yet another possibility of aptitude \times treatment \times outcome.

Although AOI research was originally developed for psychotherapy outcome research, it seems relevant to all fields of medical outcome research because therapy-related effects may be mapped onto any number of outcomes along the continuum of cure-care. In that respect then, outcomes are never ultimate. Every outcome is an intermediate step toward still another outcome (Shoam-Salomon and Hannah, 1991). For that reason, the recommendation to use multiple outcome variables in order to obtain a richer understanding of potential ATIs (Dance and Neufeld, 1988; Shoam-Salomon and Hannah, 1991; Snow, 1991) fits well within the complex systems theory approach to outcome research we advocated (Bell et al., 2002).

INTERACTION

An effect of statistical interaction occurs when the relation between two or more variables is modified by at least one other variable. Two variables interact if the effect of one of the variables differs depending on the level of the other variable. That is, the magnitude of an effect is greater at one level of a variable than at another. Statistical interaction is thus different from main effect, which is the effect of an independent variable averaging over all of the other variables.

To find out whether interaction within the experimental framework of ATI research exists, subjects are measured on some aptitude and then randomly assigned to one of two (or more) treatments. Outcome is measured on a separate variable. Regression equations are then calculated within each treatment group, using the individual aptitude measures as a predictor of the outcome. An interaction of aptitude with treatment is present when the obtained regression slopes differ (Dance and Neufeld, 1988). After determining that the

regression lines are nonparallel, various methods exist for determining range of the aptitude over which the regression lines differ significantly, specifying the exact value of the patients characteristics above which one treatment (or a package of treatments) is superior to another. For a summary review of those techniques see (Cronbach and Snow, 1977; Karpman, 1983; Rogosa, 1980).

Two types of interactions are possible: *disordinal*, meaning that treatment alternatives are differentially effective across different values of a given aptitude and *ordinal*, meaning that a given treatment is always superior to an alternative, regardless of the level of the aptitude. A disordinal interaction is apparent if the two slopes intersect somewhere within the range of the aptitude measured (Fig. 1). The example displayed in Figure 1 implies that individuals scoring high on aptitude X have a better outcome on outcome Y when given treatment A. In contrast, individuals low on aptitude X obtain better results on outcome Y with treatment B. In an ordinal interaction, one regression line remains above the others across the sampled aptitude range, but the lines are nevertheless nonparallel (Fig. 2). This result would appear to indicate that treatment A is superior for all subjects measured on the aptitude.

Although ATI is taken to refer to the greater effect and/or efficiency of a treatment in the presence of some characteristics than others, Smith and Sechrest (1991), have argued that for ATI to have both pragmatic and heuristic value (see below) the demonstration of interaction is meaningful only if it shows specificity. That is, in order to infer an interaction, it is not enough to show that a specific therapy is superior to another therapy (as depicted for example in Fig. 2). One must also demonstrate that the difference between them is smaller or larger than for some other condition. Thus, ATI research bears the minimum requirement that two treatments and two aptitudes be compared.

To better illustrate this point, consider the following example. Kalauokalani et al. (2001), hypothesized an associ-

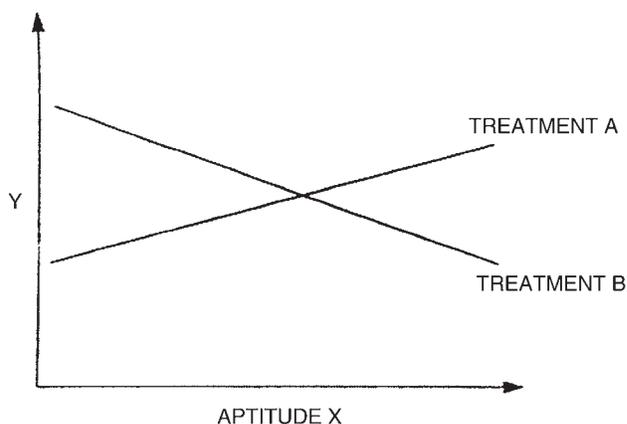


FIG. 1. Disordinal interaction, in which two slopes intersect somewhere within the range of the aptitude measured. (Adapted from Dance and Neufeld, 1998.)

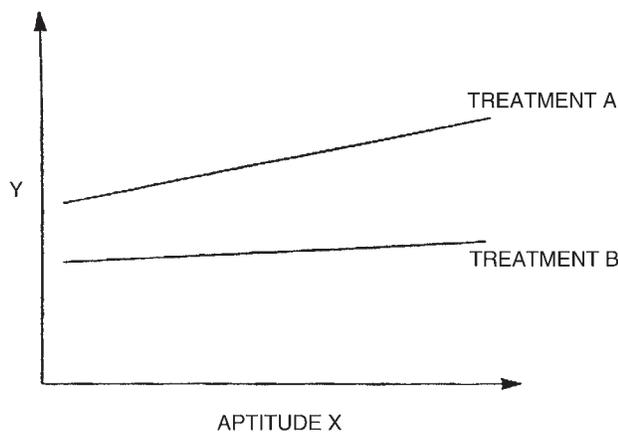


FIG. 2. Ordinal interaction, in which one regression line remains above the other across the sampled aptitude range, but the lines are nevertheless nonparallel. (Adapted from Dance and Neufeld, 1998.)

ation between patient expectation for benefit from a specific treatment and improved functional outcomes. To test this hypothesis they conducted a subanalysis of data derived from a randomized clinical trial of 135 patients with chronic low-back pain who received acupuncture or massage. Study participants were asked before randomization to describe their expectations regarding the helpfulness of each treatment on a scale of 0 to 10. The primary outcome was level of function at 10 weeks. They found that after adjustment for baseline characteristics, improved function was observed for 86% of the participants with higher expectations for the treatment they received, as compared with 68% of those with lower expectations ($p = 0.01$). Furthermore, patients who expected greater benefit from massage than from acupuncture were more likely to experience better outcomes with massage than with acupuncture, and vice versa ($p = 0.03$). The results of this study suggest that patient expectations may specifically influence clinical outcome through the interaction with the treatment itself. In contrast, general optimism about treatment, divorced from any specific treatment, was not strongly associated with outcome.

FACE VALIDITY OF ATI RESEARCH

As Shoam and Rohrbaugh (1995) suggested, “[B]oth clinicians and clients seem to ‘know’ that different folks benefit from different strokes: the idea feels right.” Smith and Sechrest (1991) also agreed that, “[C]ommon sense suggests that there should be at least some ATI in therapy.” But even if different “folks” benefit in much the same way regardless of treatment (i.e., their outcomes would be the same), they may still exhibit different change mechanisms when exposed to certain types of interventions (to be covered in Part II—Change Curves; Shoam-Salomon, 1991). Indeed, the sub-

stantial within group variation across all types of human therapy serves as ample testimony that interaction effects are an integral part of the ecology of health care (Beutler, 1991).

Findings of patient–therapy interaction provide further support for the critique of the “patient uniformity” proposition, a myth that is based on the tacit assumption that patients with a given disorder constitute a homogenous group (Dance and Neufeld, 1988; Kiesler, 1966). This myth stands in sharp contrast to the wisdom of day-to-day medicine and ATI research, both proving that therapies, patients, and providers are not interchangeable. Good medicine means individualization of treatments so that treatments are tailored and individually customized to fit the dynamic nature of the patient bio-psycho-social-spiritual makeup or profile. Aptitudes, such as personal readiness to profit from particular treatment situations (Prochaska, 1999) or perception of locus of control (Wallston et al., 1994) may render patients with similar diagnoses dissimilar with respect to both treatment and outcome. If outcome research fails to account for such differences, a potentially wrong conclusion may be made, such as in the famous case of comparative psychotherapy, where much to the disappointment of many researchers the conclusion was “everyone has won and all must have prizes” (Luborsky et al., 1975).

We mentioned previously that aptitude, as used within the ATI framework, could be related to all relevant individual differences, whether cultural, psychologic, or biologic. To illustrate how biologic differences support the face validity of ATI research, consider drug therapy. For many years medicine had no reliable ways to account for individual differences among patients. As a result, physicians prescribed approximately the same dosage of medications to everyone, young and old, men and women. There are only a few exceptions to this practice. For example, pediatric dosage is routinely adjusted for weight. Likewise, the dosage of cytotoxic medications is often adjusted to body area or height. However, it has now become evident that these simple adjustments to medication prescription are probably too simplistic. With the advent of pharmacogenomics and pharmacogenetics individual differences can finally be modeled and taken into account. Suddenly, measures such as height and weight appear to be crude, maybe even archaic. Isoenzyme phenotyping emerges as a more precise method to understand and predict drug responses. Differential response to alcohol (Room, 2001) and the case of multidrug resistance are just two examples for how individual differences moderate treatment outcomes (Goldie, 2001). It appears then that the principles of ATI are not foreign to medicine. They simply are not addressed as such.

HOW AND WHY INTERVENTIONS WORK?

As discussed above, the cluster of ATI research methods offers a way to study the effects of variables that mediate

outcomes such as patient aptitudes. Accordingly, ATI research seeks to understand questions such as, who does and does not benefit from a specific treatment? Would the patients who do not benefit from one treatment benefit from another treatment? Would patients who do well under one treatment benefit less if assigned to another treatment? Are treatments for well-matched patients more effective than treatment for poorly matched or randomly assigned patients? (Shoam and Rohrbaugh, 1995). Symmetrically, ATI research may also be useful for detecting interventions that are harmful (Ridenour et al., 1999).

Thus, ATI research may have both heuristic and pragmatic values. Heuristically, ATI research promises to provide information that would result in a better understanding of the mechanisms that underlie the outcome achieved by the administration of different treatments to different individuals. That is, ATI research may help advance knowledge about the nature and course of clinical disorders and hence impact theory development. Pragmatically, ATI research aims at providing information that would result in optimal matching between different patients (based on their aptitudes) and different treatments in order to maximize treatment efficiency and effectiveness. Thus, by identifying components of an intervention that are more or less effective under different conditions ATI research may help determine the type of interventions that need to be adapted in order to fit local needs and to increase the potency and cost-effectiveness of care (National Institute of Mental Health, 2002). In Part 2 of this paper we will discuss how exactly this can be accomplished.

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Address reprint requests to:

Opher Caspi, M.D., Ph.D.

Program in Integrative Medicine

Department of Medicine

College of Medicine

The University of Arizona—Health Sciences Center

P.O. Box 245153

Tucson, AZ 85724-5153

E-mail: ocaspi@ahsc.arizona.edu

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