Chapter 6
Application of the Single Subject Design in Biomedicine

Although there is a long tradition of employing single subject designs in social science research, these designs have only recently been utilized in biomedicine. The single subject design methodology has been overlooked in biomedicine, even though physicians are essentially conducting single subject (N-of-1) trials when conducting patient care (i.e., treating a patient). This research design can be used to study the time course, variability, or effect of an intervention or treatment on a single patient [1]. In a primary care setting, the patient generally exhibits symptoms and the physician follows evidence-based or appropriate steps to treat these symptoms. The physician evaluates the patient's history, signs, symptoms, medical test results, and examines the patient, and subsequently implements a treatment or intervention if warranted. In order to determine treatment effectiveness, the symptoms are later examined to determine if they are ameliorated or eliminated. In primary care settings, standardized procedures are employed that include objective measurement of the outcomes, such as systolic blood pressure measurements. These design and intervention procedures are analogous to the standardized procedures used in single subject research designs, such as testing the effectiveness of a medication over a course of time. Specifically, Janosky [1] has demonstrated the applicability of the single subject design to primary care practice-based research. This chapter highlights both past and current uses of single subject designs in biomedicine. In addition, an overview of the procedures for conducting a study will be illustrated through biomedical research examples, and finally, an annotated bibliography in Chapter Seven contains refereed publications included as a systematic review.

Past and Current Application of the Single Subject Design in Biomedicine

Research in biomedicine appears to rely on randomized parallel group clinical trial designs and considers these trials the "gold standard" when determining treatment effectiveness. However, large-scale trials contain inherent limitations in that they can be expensive and time consuming. In addition, patients are unique and may not respond similarly to various treatments, and in those instances a randomized clinical

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trial design may be inappropriate. Guidelines are established from the averaged study findings, which may not necessarily be applicable when evaluating suitable treatment options for individuals [1]. Specifically, patients treated in primary care settings may differ clinically from patients in the clinical trial, the patient diversity in the clinical trial may not generalize to certain patient populations, and the stringent trial criteria for accepting participants may not accurately reflect general patient populations [1]. This is an important consideration as the field of biomedicine strives to pursue cultural competency. Single subject designs also provide greater flexibility for treatments, as ineffective interventions can be modified over the period of study [2]. Thus, single subject designs should be considered when conducting research in biomedicine, as the methodology and interventions can be tailored for specific individuals. In recent literature, it appears these designs are receiving more recognition, as they are being increasingly employed in research across disciplines [3].

Treatments are often unavailable for unique patient populations or rare disorders, and researchers are left uncertain what designs or tools to use when implementing treatments. In response to these issues, an Institute of Medicine committee created recommendations for conducting trials with small sample sizes. This report, *Small Clinical Trials: Issues and Challenges* [4], discusses guidelines for using single subject designs. Small clinical trials should be considered for rare diseases, along with unique study populations when clinical trials would not have a sufficient sample size to provide adequate power. If clinical trials do not have sufficient statistical power, or a large enough sample, then researchers are unable to determine treatment effects with a high degree of certainty. Single subject designs are warranted in situations when the standard approach to clinical trials is not feasible, such as with unique patient populations, public health urgency, and emergency situations [4]. Small clinical trials are also appropriate for individually tailored therapies (e.g., managing hypertension, diabetes) and within isolated environments.

As was presented in Chapter 1, in the 1980s, McMaster University [5] designed a service for community and academic physicians to facilitate the planning and conduction of single subject (N-of-1) trials. The effectiveness of the trials was evaluated by the physicians' management plans and confidence levels in the plans both prior to and following trials. A total of 57 single subject trials were completed, with 50 trials providing a definite clinical answer and 15 resulting in the physician altering patient treatment. In those 15 trials resulting in treatment adjustment, 11 trials lead to physicians discontinuing the medication therapy they planned to administer indefinitely. Trials that were not completed generally stemmed from patient' or physician' noncompliance or patient' concurrent illness. From this service evaluation, the collaborative team at McMaster University [5] concluded that single subject trials would be useful for providing treatment in clinical settings.

More recently, researchers in Australia developed a single subject (N-of-1) trial service for physicians that was used to examine the effectiveness of stimulants for AD/HD treatment [6]. The premise of its development was to lessen the challenge of predicting which children would respond to stimulant medications and various dosages. Thus, the service allowed flexible dosing, compared to implementing fixed dosages by weight, and it also used multiple crossovers, rather than

only one. Patients included in the trial service were children between the ages of 5 and 16 who were clinically diagnosed with AD/HD, and in the past were stabilized with an optimal stimulant dose. These patients were selected because past treatment effectiveness was questionable. The design consisted of a within-patient randomized, double-blind, crossover comparison of stimulant (dexamphetamine or methylphenidate) versus placebo or alternative stimulant, with 3 treatment period pairs. Since access to services is limited in Australia due to geographically spread of communities, trials were conducted from a central location through mail and telephone communication. Measures used to evaluate treatment effectiveness included the number of patients recruited, number of doctors who used the service, geographic spread, completion rates, response rate, and N-of-1 decisions following the trial. Out of 45 physicians requesting 108 N-of-1 trials, 86 trials were completed. Immediately following the trial, 19 of 25 drug versus placebo responders continued taking the same stimulant, while 13 of the 24 individuals that did not respond discontinued or switched stimulants. Of those in which data were available, in 40 of the 63 patients, posttrial management was consistent with trial results. In all of the trials combined, management changed for 28 of 64 patients for whom information was accessible. The authors concluded that N-of-1 trials targeting AD/HD symptoms can be employed successfully through mail and telephone communication and they are also valuable for examining intervention effects.

Numerous studies have highlighted the importance of the single subject design paradigm in primary care. for example, Powers et al. [7] evaluated behavioral and nutrition treatment in children with cystic fibrosis using a changing criterion single subject design. The intervention consisted of a 5-week long nutrition counseling and child behavioral management training for parents. The aim of this investigation was to increase the amount of calories consumed each day, in order to improve energy levels. Ten families were randomized, in which four were assigned to the behavioral and nutrition treatment and six families were included in the usual care control condition. The researchers found the intervention was indeed successful, as total daily caloric intake increased only in the presence of the treatment.

Single subject designs have been effective in treating patients with diabetes, especially for altering pharmaceutical dosages. Tsapas and Matthews [8] discussed that N-of-1 trials can be an optimal approach when treating chronic diseases such as diabetes mellitus, which frequently rely on clinical judgment and arbitrary criteria. The authors stated that guidelines for treating diabetes have been criticized as being unreliable, as algorithms are generally established from “clinical judgment and experience.” Single subject designs take into account the uniqueness of the individual, rather than using a standarized treatment that may not be effective for all diabetics.

A large portion of research studying treatments for aphasic patients relies on single subject designs. In response to the popularity of the single subject design, Beeson and Robey [9] evaluated the “lessons learned” from its use in the aphasia literature. This article presented situations where researchers should use single subject designs versus large clinical trials, and researchers are advised to initially examine new treatments with a small number of patients, rather than using large-scale studies.

Next, additional studies should be created as follow-ups, which can adjust or refine the methodological procedures, discern the most appropriate candidates, and continue to determine the potential efficacy of the treatment. If results appear promising from the pre-efficacy studies, then well-controlled group designs can examine treatment efficacy using controlled conditions. In essence, large-scale research studies should be conducted once techniques are sound and results have positive outcomes. If a treatment demonstrates to be efficacious, then research should ensue to evaluate the impact of treatment under conditions of service delivery, which translates to effectiveness. A cost-benefit analysis could be included as a final phase. In addition to the aforementioned steps, Beeson and Robey [9] presented an approach to quantifying results from single subject designs using effect sizes, since there is debate that solely evaluating data with visual graphs can lead to error (See Chapter 4).

There is utility in using the single subject design in a multitude of fields. Recently an editorial by Rapoff and Stark [2] appeared in the *Journal of Pediatric Psychology*, with the goal of encouraging researchers to submit research employing single subject methodology to this journal. Specifically, the authors reviewed designs appearing in the pediatric psychology literature and discussed how single subject methodology can be useful for promoting the mental health, health, and quality of life of children, along with advancing research in the field.

The broadened use of single subject research designs could have a significant impact in primary care and biomedicine. The application of single subject designs can be presented for instruction to biomedical students, residents, fellows, and medical research faculty and practitioners. Increasing awareness of this design can enhance the researcher's repertoire and expertise of research methodologies available for treating patients and developing research designs. As indicated by the National Institutes of Health (NIH) Roadmap (NIH Roadmap Initiative [10]), there is a need to establish programs that train individuals to conduct research with sound methodological designs. Under the leadership of Dr. Elias A. Zerhouni, NIH created the Roadmap initiative [10] with the overarching goal to accelerate the pace of discovery in the life sciences and the translations of effective therapies from bench to bedside. Scientific advances are made from the interface of traditional disciplines with integrative investigators from diverse research backgrounds, and the utilization of interdisciplinary research encompasses the strengths of two or more diverse scientific disciplines working collaboratively to research a scientific inquiry. A basic tenet is that researchers involved in the Clinical Research Workforce Training should be engaged in all aspects of clinical research, which will lead to studies containing tenable research methodology. In order to successfully produce studies of sound quality, future investigators are admonished to understand the issues and to acquire the necessary research skills. Single subject designs are an innovative addition to the arsenal of available methodology for addressing biomedical research inquiry. This design has the potential to be applied more readily for appropriate research questions, particularly for community-based research, and as a methodological research tool for the NIH Roadmap designed "Research Teams of the Future" [10].

As with any research design, there are inherent limitations associated with single subject studies. There may be limits in generalizing the findings, such as the

effectiveness of an intervention or the size of the benefit, across populations of patients [1]; however, replication of treatment results across a series of patients can increase confidence in generalizability. Another potential weakness lies with the options for inferential statistical analysis, as these are unlikely to be valid or available for single subject designs [12, 13]. Nonetheless, there are other more valid statistical methods available for treatment evaluation, such as the nonparametric smoother [11, 12]. Despite the limitations of the single subject design, tenable and accurate tests of intervention effectiveness can be conducted with patients.

Overview for Conducting a Single Subject Design

This section provides an overview of the methodology and steps involved in carrying out a single subject design. The application of a single subject research design, as in implementation of all research designs, must begin with the research question of interest. These questions could include investigating how a treatment would affect an outcome; for example, how an antihypertensive medication will impact blood pressure levels. The intervention or treatment (i.e., independent variable) and outcome (i.e., dependent variable) must be operationalized. The independent variable is considered to be an intervention (e.g., blood pressure medication) and the dependent variable is the variable of interest or the outcome (e.g., diastolic and systolic blood pressure measurements). In biomedicine, the dependent variable could encompass outcomes like the clinical impact, laboratory values, intensity, number, or duration of a symptom, and so forth. The choice of the outcome must be driven by the study goals, as well-controlled outcome measurements are analyzed over a period of time. Methods for measuring and recording outcomes could entail observation, self-report, clinical assessment, and physiological measurement among others [14]. Strengths and weaknesses of various methods should be explored. For instance, reactivity could occur with self-monitoring and observation of behavior [15]. In addition, the researcher would also determine the frequency and structure of assessing the outcomes, such as whether to record outcomes daily, weekly, or under what environmental setting. Measurements should be standardized and baseline phases should be identical to procedures employed during the intervention [16]. Since single subject designs rely on examining the progression of outcomes over time, continuous assessment of outcomes is essential. Multiple outcome measurements allow for examination of the patterns and stability of the outcome or dependent variable. Inferences can be drawn from analyzing outcomes patterns between the time a treatment is withheld, implemented, altered, or removed. This allows the researcher to generate accurate inferences regarding sources of variability on the outcome, particularly when alternating experimental designs are used.

The cardinal rule when implementing an intervention is to change one variable at a time throughout each phase, in order for intervention effects to be evaluated independently [14]. The physician or researcher should identify a criterion for successful treatment a priori to determine the effectiveness of the intervention. If an

intervention is not successful in promoting change during the intervention phase, the intervention can be altered or a new treatment phase may be implemented [17]. Examples of interventions may include pharmaceutical therapy for hypertension or insulin therapy for blood glucose control.

Baseline (A-phase) phases are useful within single subject design, in that the occurrence of the outcome can be measured prior to the employment of an intervention. The baseline phase can be used for comparative purposes with the outcome measurements of the remaining phases, such as the treatment (B-phase). Baseline measurements are generally recorded prior to intervention implementation. Baseline data serve as a standard of current performance that can be compared to future changes in the outcome [14, 17]. There are no strict guidelines for determining the length of time for measurement; however, it is suggested that five to seven measurements occur within the A-phase, or measurements be continued until stable [12].

Strengths and limitations of particular designs should be acknowledged prior to study implementation. For example, as discussed in Chapter 3, although the A-B design is simple to use in clinical settings, a disadvantage is that it cannot control many threats to internal validity, like maturation, history effects, testing effects, and instrumentation [20]. For example, with maturation effects there is potential for the developmental changes of a patient to alter along with the treatment. Also, there are many issues pertaining to treatment withdrawal in an A-B-A design. As reviewed in Chapter 5, ethical concerns exist when withdrawing treatment, as the patient is no longer receiving potential benefits of the treatment; however, intervention withdrawal is frequently necessary in order for attributing outcome improvement to the intervention. Multiple factors are frequently involved in this decision-making process, such as time limitations, staff cooperation, and ethical considerations [14]. In the event that treatments are withdrawn during the study, participants are generally offered the full treatment benefits following the conclusion of the study.

When analyzing treatment effectiveness across the study phases, a number of methods can be employed for determining change in the outcome, as reviewed in Chapter 4. Visual analysis through graphical representation of the data is commonly used. Komaki, Coombs, Redding, and Schepman [18] recommend using a set of criteria for evaluating single subject design data, referenced with the acronym "OCT". The overlap (O) in data points should first be examined between phases, next the measure of central tendency (C) for each phase is calculated, and subsequent outcome trends (T) are analyzed. When analyzing data visually, researchers should first examine data within conditions or phases, including the number of data points, variability, level, and trends. Following data inspection within phases, data analyses between conditions should be continued using the same criteria (i.e., number of data points, variability, and trend) [18]. In addition, if a clinical criterion was established a priori, the overall evaluation may determine whether outcome levels reached this criterion, such as a sustained target of systolic blood pressure measurements (e.g., 110 for systolic blood pressure). However, researchers should be cautioned against solely relying on visual inspection of data since subjectivity may be heavily involved. Consequently, time-series analysis, curve fitting, the C statistic, analysis of variance (ANOVA), among others, have been suggested as alternative methods

for data analysis [11]. The split-middle technique could also be applied, which combines the graphical display of data and formal statistical inference, as it fits a straight line to data points within phases [19, 20]. Parametric statistics can provide greater clarity in cases of intra-subject variability [13]; however, due to assumptions of traditional statistical tests being frequently violated, these statistical methods may be inappropriate in many situations [11]. Within the single subject paradigm, the nonparametric smoother [21] has been proposed as a more appropriate method for analyzing data, as it does not contain statistical restrictions inherent in parametric tests [11, 12].

Illustrations of Single Subject Design Application

Example 1

Figure 6.1 contains a display of data representing results from a single patient study. The patient was a 52-year-old Caucasian, female who was nonobese. Presented are data for glucose intolerance, insulin response to oral glucose, and insulin resistance. Two different doses of a glucose load were administered orally in treatments 1 and 2. Glucose intolerance and insulin response to oral glucose are the areas under the

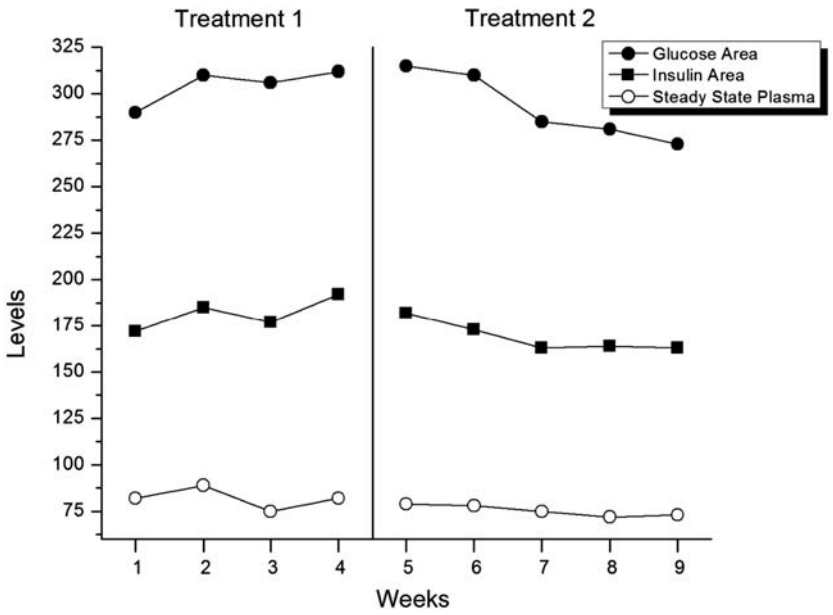

Fig. 6.1 An alternating treatments design is presented targeting glucose area, insulin area, and steady state plasma glucose

straight line connecting glucose and insulin levels. These outcomes were determined from blood samples drawn during a three hour glucose tolerance testing following treatment administration. Steady state plasma glucose was the measure of insulin resistance, as determined after the chemical suppression of endogenous insulin secretion. Measurements are presented for one-week assessments both before and after a change in the dosage of an oral agent.

During the development of this study, the researcher likely had a goal or question that provided direction during the decision-making process. The investigation analyzed the effects of two different doses of a glucose load on glucose area, insulin area, and steady state plasma glucose. Since the design included one type of intervention, the main research question was if different dosages would differentially influence the target outcomes. The investigators decided on using three outcomes that were measured simultaneously throughout the course of the study. An alternating treatments design was employed without a baseline phase. Baseline phases are preferable in single subject designs, as the occurrence of the outcomes can be later compared with outcomes derived from intervention implementation. However, there are situations when a baseline phase may not be unnecessary or not feasible. A baseline may not be warranted if there is urgency for providing treatment to a patient, or if the study has financial or time constraints.

Standardization of the procedures and timing of measurement is also essential, in order to decrease the impact of extraneous variables on the target outcomes. These researchers gathered outcome measurements on a weekly basis. Specifically, blood samples were drawn during a three hour glucose tolerance testing following treatment administration. The procedures and environmental setting for gathering the outcome measurements were consistent week to week. A lack of standardization, such as varying the time of gathering the outcome measurements, increases the potential for procedural alterations to affect the measurement, rather than the intervention alone. Also, continuous assessment is crucial when conducting a single subject design, as trends in the data assist researchers in determining intervention effects. If there are too few data points within a phase, uncertainty of the trends or treatment effects can occur. As illustrated in Figure 6.1, this particular study analyzed the first intervention, or glucose dose, over a course of four weeks, whereas the second intervention, or dose alteration, was examined over a period of five weeks. Multiple data points in each phase allowed for trends to be analyzed both within and between intervention (B) phases. Phases should be continued until data trends are fairly stable. As shown in Figure 6.1, the target outcomes of glucose and insulin area gradually increased during the first intervention phase, with the exception of the small dip between weeks 2 and 3. Examining the outcomes in the second intervention phase, in which the dosage was altered, there was a slightly steeper decrease in glucose area compared to insulin area levels. Referring to the steady state plasma data points, levels remained relatively stable within and across both interventions. Taking this visual analysis into account, it appears the first dosage resulted in an increase of glucose and insulin area levels, whereas the second intervention was responsible for a decrease in these outcome variables. In terms of statistical analyses, a split-middle technique could be employed in this example, in which a straight

line is fit to the data points within phases. The nonparametric smoothing method could also be used for examining the time series of data points.

Example 2

These data represent the results from a single patient study. The subject was a 19-year-old African-American, female university student being treated in a psychiatric care facility for anorexia. Figure 6.2 presents data for total calories consumed each day (i.e., daily total caloric intake). The conditions reported included the on-admission/baseline (days 1–3), active pharmaceutical intervention (days 4–18), active pharmaceutical and behavioral intervention (days 19–32), and monitoring until discharge (days 33–45).

During the development of this study, the research goal was the investigation of which interventions would be most effective for increasing daily caloric intake. Food consumption was monitored over the course of the study, particularly the accumulation of calories consumed each day. The study examined the intervention (B) effects of an active pharmaceutical intervention versus the identical pharmaceutical treatment with the inclusion of a behavioral intervention. Baseline phases (A) were also

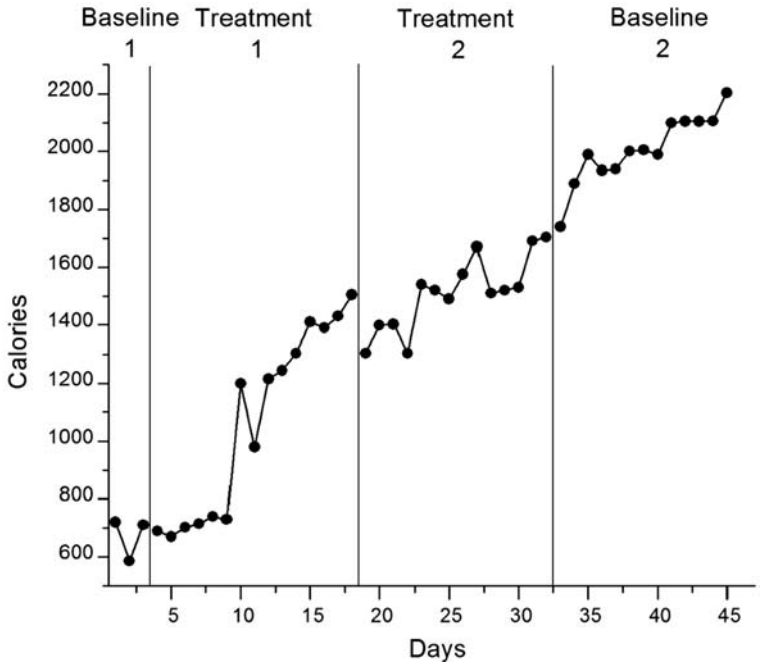

Fig. 6.2 An A-B-B-A design illustrating the course of treatment for an anorexic patient with caloric intake as the outcome variable

included to determine the daily caloric intake, which could be used for comparison of caloric intake during the two interventions. Specifically, this study is an A-B-B-A single subject design. The initial phase was employed prior to any of the treatments and likely reflected the patient's regular caloric intake in her environment. The final baseline phase included withdrawal of both interventions, as the investigator sought to study whether the intervention effects would continue with absence of treatment. In single subject designs, this second baseline phase, considered a reversal, is generally an attempt to revert the outcome variable to initial baseline levels [20, 22]. However, it is not always plausible that an outcome will revert to its original levels following withdrawal of an intervention, especially in this case, as interventions can contain long-lasting effects. There are also ethical concerns when withdrawing treatments that are potentially beneficial, but it is often a necessary condition for determining treatment effectiveness. In this particular case, perhaps the investigators were interested in knowing whether the patient would maintain a healthy caloric intake without interventions; that is, the treatment benefits may continue to exist following the intervention withdrawal. Furthermore, the researchers could have also been testing patient stability prior to discharging her from the inpatient clinic. Ethical concerns can be ameliorated through offering a continuation of treatment services following termination of the study. In this example, however, Fig. 6.2 reveals that the final baseline phase did not produce any apparent adverse effects, as the patient's daily caloric intake continued to improve.

As in all single subject designs, it is crucial that procedures are standardized for greater experimental control. The researchers in this study chose to measure caloric consumption over the course of the day. Each day, total calories were used as the target outcome of measurement. The length of each phase was also important in this study. In general, the phases should be continued until outcome trends are stable and contain little variability. As displayed in Fig. 6.2, the initial baseline phase only contained three daily measurements. It is likely the patient was in great need of an immediate intervention, as her daily caloric levels were extremely low and unhealthy. Next, between days 4 and 18, the first pharmaceutical intervention was employed. This phase contained several data points that could be used for drawing treatment inferences. Figure 6.2 shows that the initial six days of the first intervention produced little change in the patient's daily caloric intake; however, there was a sharp increase in caloric intake between days 9 and 10, which led to gradual, steady increases for the remainder of the phase. It is possible the medication effects were slow initially and required a few days to make a significant impact. The second treatment phase continued to include the pharmaceutical intervention, but also added a behavioral intervention. Since the medication intervention was continued, the investigators were likely examining if there were added benefits to employing a behavioral treatment. However, the effects of this added intervention should be interpreted with caution, as medication effects interacted with this intervention and could have contributed to potential outcome variation. In this example, a comparison of trends within each treatment could be examined with the split-half method or possibly other statistics. As shown in Fig. 6.2, steady treatment gains appear not only within the second intervention phase, but also in the final baseline phase

of monitoring daily caloric intake. Visual inspection of this graph reveals that the interventions produced considerable change in the daily caloric intake of an anorexic patient. In addition, previously discussed statistical methods could be employed for further data analysis.

Example 3

These data represent the results from a single subject A-B-B design. The patient was a 7-year-old, mixed race (African-American and Caucasian), male who was being treated for an obsessive compulsive behavior of head banging. Reported is the duration, in minutes, of the first incident reported per day. The treatment was administrated by the patient's father, with the conditions of baseline (days 1–7), active behavioral intervention (days 8–17), and active pharmaceutical and behavioral intervention (days 18–52).

In this example, the research question was whether two differing interventions (behavioral intervention versus both behavioral and pharmaceutical interventions) could decrease the duration of the initial daily episode of head banging. The patient's father monitored and recorded the number of minutes the patient initially engaged in head banging activity each day. The researchers selected an A-B-B design for this subject. For the first seven days, the patient's head banging activity was recorded in the absence of any interventions. Figure 6.3 displays the various phases in this design. Referring to the first baseline (A) phase, the patient's initial duration of head banging activity each day ranged between 40 and 50 minutes. Following baseline stability, the first treatment phase of active behavioral intervention was employed. The father was instructed regarding the study and intervention procedures. He likely had frequent contact with the patient, as the outcome measurement included the first incident of head banging activity each day, recorded in minutes. This behavioral intervention occurred between days 8 and 17, which provided a number of data points that could be used for trend analysis. Figure 6.3 shows that in the first intervention there was an initial increase in minutes of head banging activity in comparison with the baseline levels. This increase could be due to the patient's reaction to the new intervention or other extraneous variables. Nonetheless, there was a sharp decrease in head banging duration between days 8 and 11, which subsequently resulted in a more gradual, steady decrease. The second intervention phase was introduced at day 18 and continued until day 52. This second intervention retained the first behavioral intervention and added a new pharmaceutical treatment. The investigators examined whether including a medication treatment would alter outcome trends, further decreasing head banging activity. Referring to the second intervention in Fig. 6.3, it appears that the outcome continued to decrease over the course of the phase. It is difficult to ascertain, however, whether the behavioral intervention or pharmaceutical intervention had a greater impact on the outcome decrease. An issue with single subject designs is that researchers must decide the order of the interventions. Since residual effects of treatments linger even follow-

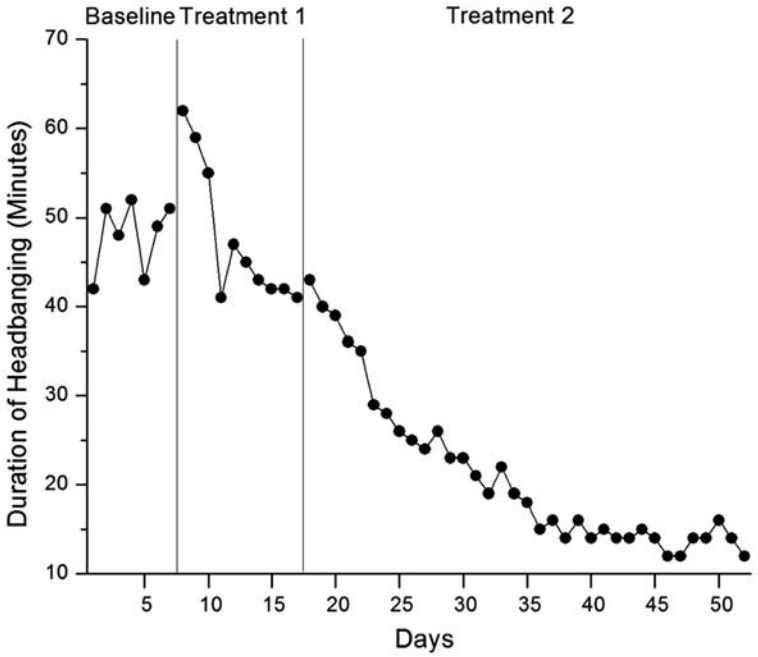

Fig. 6.3 An A-B-B design displaying the duration of head banging activity each day through the inclusion of a baseline phase and two differing treatment phases

ing treatment reversals, it is challenging to obtain a pure measure of the second intervention's effects. This problem is essentially why continuous assessment is important, as researchers rely on data trends when examining treatment effects. Nevertheless, results of this study revealed that both interventions were equally successful in reducing duration of head banging behavior. To further examine the data, median coordinates could be calculated within each phase and a split middle technique could plot data trends. Other statistics, such as an analysis of variance (ANOVA) could be employed for comparative purposes; however, inferences should be made with caution since statistical assumptions are violated. Overcoming these statistical limitations is the use of the nonparametric smoothing technique [12]. As such, the parametric smoothing technique could be used to examine trends between phases [12].

There are several issues the researchers likely considered throughout the course of this study. First, the patient's father was responsible for implementing the interventions and recording the duration of head banging activity. There is less experimental control in this example, as the researchers or physician trusted the patient's father would be compliant with adhering to the standardized procedures of the study. If the father was inconsistent with the treatment protocol, the study's internal validity would be threatened. Specifically, changes in the outcome may be attributable to errors in measurement recording or inconsistency in treatment implementation

(e.g., weak medication adherence). In addition, the patient's behavior could have varied by being aware that his head banging behavior was being recorded. Also, the study setting took place in the patient's home, which is an uncontrolled setting. There are strengths and limitations associated with the home setting versus a controlled laboratory setting. Although experimental control is extremely important when conducting single subject designs, there are instances when the occurrence of a behavior may not be observable in a more sterile, controlled setting. The patient may not display the same duration of head banging behavior outside of the home. Also, since the problem appeared to occur within the home setting, it would be reasonable to give intervention instruction to an individual who has frequent contact with the subject. Other threats to internal validity include maturation effects, as the natural development of the patient could have potentially lead to outcome variation; however, in this particular study, it is inferred that this was not an issue since the initial baseline levels were fairly stable.

Example 4

These data represent the results from a single patient study. The subject was a 42-year-old, mixed race (African-American and Asian), male who was treated for elevated blood pressure. The conditions were daily measurements (following breakfast) of diastolic and systolic blood pressure (mm Hg) during baseline (days 1–7), active pharmaceutical-dose 1 and dietary intervention (days 8–15), along with active pharmaceutical-dose 2 and dietary intervention (days 16–31).

The research question through this illustration involved testing the impact of two differing interventions (behavioral intervention versus both behavioral and pharmaceutical interventions), specifically whether these interventions would decrease elevated systolic and diastolic blood pressure levels. The researchers first determined that the outcomes would consist of systolic and diastolic blood pressure. The frequency and timing of the measurement was also considered. Important data may not be gathered if there are long latencies between measurements. Consequently, daily measurements were obtained under standardized procedures, reducing outcome variability from extraneous variables outside of the study. For example, blood pressure levels may alter depending on the time of day and the level of activity; thus, it is important to obtain consistent measurements during the same time of day. In this example, the investigators chose to gather measurements following the patient's breakfast. During the initial baseline (A) phase, daily blood pressure measurements were recorded for 7 days in the absence of any interventions. Figure 6.4 displays that the blood pressure levels were quite high, yet relatively stable in the baseline phase. The first treatment phase (B) was introduced between days 8 and 15, which contained an active pharmaceutical-dose 1 and dietary intervention. In the first treatment phase, notice the gradual decline in both systolic and diastolic blood pressure. This intervention was continued for a number of days, which was useful for analyzing trends over time. Next, the second treatment phase (B) was implemented

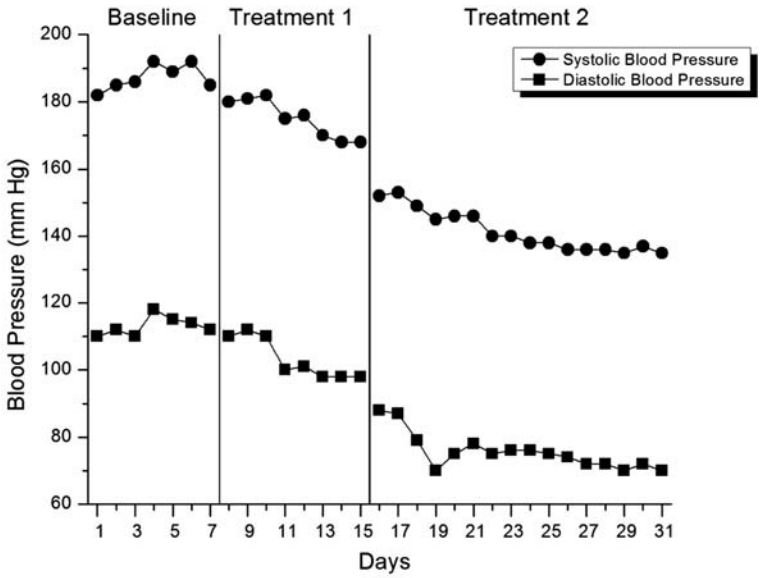

Fig. 6.4 An A-B-B design illustrates interventions for reducing elevated systolic and diastolic blood pressure levels

between days 16 and 31. This second intervention also included a dietary intervention; however, the pharmaceutical dose was altered from the previous intervention phase. Figure 6.4 shows that a significant decrease in blood pressure levels occurred immediately within the second intervention. Specifically, at the conclusion of the first intervention, blood pressure levels were 168/98 and at the introduction of the second intervention levels sharply decreased to 152/88. The decrease in both systolic and diastolic blood pressure continued over the course of the second intervention phase. As in the first intervention, systolic blood pressure in the second treatment phase declined steadily. There was greater variability in diastolic blood pressure within the first few days of the second intervention. A sharp decrease is shown in Figure 6.4 between days 17 and 19; however, the next few days resulted in a slight increase, followed by a gradual decrease over the remaining duration of the phase.

It is challenging to disentangle the added benefits of the dietary intervention from the pharmaceutical intervention in this study, considering they were employed concomitantly. If the researchers were interested in understanding the impact of the dietary intervention alone, this intervention could have been enforced following the baseline, prior to the implementation of a medication; however, it is likely the researchers had the overarching goal of analyzing the differential impact of medication dosage on blood pressure. Perhaps the dietary intervention was used for stability purposes, as variability in diet could potentially influence blood pressure. Experimental control is crucial for any experimental study. There are also several validity issues the researchers may have considered. For one, medication adherence

is important, as missed doses could alter outcome levels. In addition, the method of obtaining blood pressure would need to be standardized. Blood pressure standing versus sitting could confound results. The researchers would have implemented detailed procedures that were consistently used throughout the study, such as recording blood pressure levels while the patient was sitting. Overall, it appears that both interventions were successful in decreasing high blood pressure levels; however, visual analysis of the graph reveals the second medication dose may have been more effective than the first intervention.

Summary

The single subject design has been successful in illuminating research findings across a variety of disciplines. It overcomes some of the inherent limitations found in large-scale clinical trials, in that treatments are tailored for unique individuals and can also be modified over time. Research supports the effectiveness of the single subject design, from studying treatments for rare patient populations to providing N-of-1 trial services in assisting physicians. The single subject design is an innovative addition to the arsenal of available methodologies for primary care physicians, biomedical students, residents, medical research faculty, clinical practitioners, among others. Consistent with the NIH Roadmap Initiative, increasing awareness of the utility in the single subject design could enhance treatment approach and evaluation both in biomedical research and primary care settings. The annotated bibliography, presented in Chapter 7, identifies single-subject design articles published in PsycInfo, MEDLINE, and PubMed.

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