

Drug Compliance by Adolescent and Young Adult Cancer Patients: Challenges for the Physician

Benjamin Gesundheit • Mark L. Greenberg •
Reuven Or • Gideon Koren

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22.1 Introduction

The terms *compliance* and *adherence* describe the behavior of following advice or instructions, and these terms are used interchangeably. In the medical context, compliance refers mostly to drug intake, but may also include adherence to diet, lifestyle, and other therapeutic modalities including medical follow-up. Noncompliance can be manifested as failure to fill the prescription, failure to take the prescribed drug, and incorrect frequency, timing, or dosage of drug administration. Correctly defined, misunderstanding the instructions of the health-care provider does not constitute noncompliance, but since this reason is raised frequently by the patient, a striking lack of understanding may reflect an underlying problem of noncompliance. Likewise, refusal of treatment might be considered as noncompliance at its extreme, as the case of the 13-year-old boy Tyrell Dueck, who refused treatment for osteosarcoma [1], even though the total lack of agreement to accept any treatment is a different issue.

Compliance may imply acceptance and accommodation to a dominant force (i.e., the physician dictates and the patient accepts). In the current climate of practice, however, the treatment process is ideally a partnership between the patient and the health-care providers, and therefore, compliance has to be redefined as an agreement between the patient and his health-care providers to restore or maintain the patient's health [2]. The best definition for compliance is the extent to which the patient's behavior coincides with medical or health advice [3–4].

Lack of compliance transcends the boundaries of disease categories and age groups. The number of research articles on patient compliance increased from 15 per year in the mid-1970s to more than 100 per year in recent years [5]. Although an abundance of literature is available on compliance issues in the adult cancer patient, little research exists on compliance of children [6, 7], and particularly of adolescents with cancer [8, 9].

The clinical implications of poor drug compliance are enormous. Noncompliance with oral chemotherapy may play a role in the long-term prognosis of childhood leukemia [10, 11], in the relapse rate [12–14], and in the graft survival after transplantation [15]. The prednisone nonadherence rate in adolescents and young adults with acute lymphoblastic leukemia (ALL) or Hodgkin disease was 52% according to the measured drug levels [12, 16]. The noncompliance in adolescent outpatients with cancer was 59% [11]. In a study of compliance using blood levels of 6-mercaptopurine in children with ALL, one-third of patients had undetectable levels of drug [14, 17]. The rate of compliance in pediatric and adolescent patients with cancer ranges from 40 to 60% [9]. With the advent of more successful treatment for childhood and adolescent cancer, the compliance factor is gaining greater importance because therapy is given currently with curative, rather than only palliative intent.

Thus, the implications of poor drug compliance by teenagers with cancer are enormous, and preventing this major factor of therapeutic failure is a paramount challenge for clinicians. Furthermore, the compliance of physicians and their prescription pattern of maintenance chemotherapy in ALL may contribute substantially to the success or failure of treatment, and improved physicians' compliance may improve the prognosis of the disease [18]. In order to understand the behavior of drug compliance, it is important to realize that for the adolescent with cancer, very often it is not survival of the disease in the future, but rather survival of the treatment in the present that is crucial [19].

Strict adherence to chemotherapeutic protocols is essential to secure optimal outcome. In clinical trials, noncompliance may lead to an overestimation of required dosage and may lead to significant toxicity

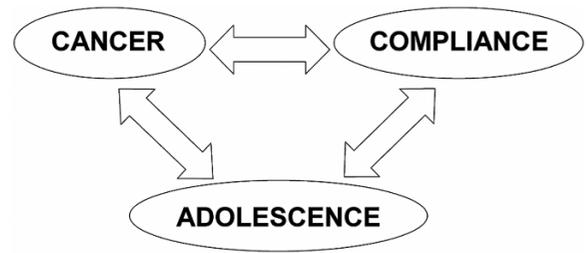


Figure 22.1

Cancer, adolescence, and compliance

and morbidity if drug dosage is increased because of perceived lack of response, or if the compliance of a patient suddenly improves. Drug noncompliance may obscure the actual rate of adverse reactions and may lead to a waste of resources. The availability of venous access ports and easy-to-operate pumps make the administration of parenteral chemotherapy at home (“home care”) possible, but this introduces a new dimension to the issue of noncompliance.

22.1.1 Compliance: Definition and History, Cultural Changes During the Last 50 Years

Historically, Hippocrates (470–410 BCE, Greece) expressed in his famous oath his concerns about patients' noncompliance: “Keep watch also on the fault of patients which often make them lie about the taking of things prescribed” [20, 21]. Compliance with drug therapy for acute diseases and symptoms is often better than for chronic diseases [22]. Along with these therapeutic goals, social and legal changes of rights and the autonomy of the patient have caused major changes in the patient–physician relationship (PPR). The involvement of the patient and his consent for treatment is crucial, and nowadays no therapeutic modality is conceivable without the full cooperation of the patient.

Research on compliance focused initially on non-compliers and on the reasons for failure to adhere to instructions about medication given by patients: inadequate supply of medication, forgetfulness, misunderstanding of instructions, errors, discontinuation of treatment because symptoms have cleared, resistance

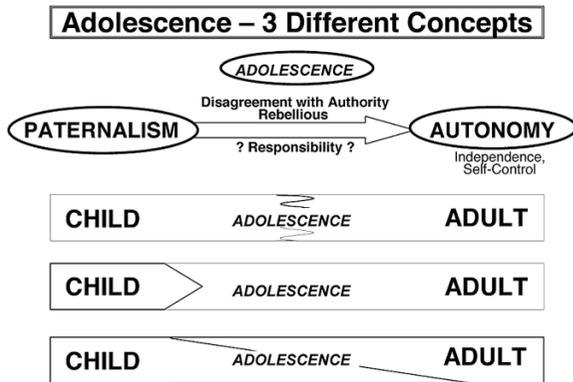


Figure 22.2

Childhood, adolescence and adulthood – three different approaches

of the child, apparent ineffectiveness of the medication, or side effects [23]. More recently, research has aimed to identify the risk factors and predictors of noncompliance by more objective measures.

22.2 Conclusions

22.2.1 Cancer, Compliance, and Adolescence: Definitions and Interactions

The diagnosis of cancer has major effects on the patient's life. The fear of death and the severe adverse effects of treatment cause major stress for the patient and his family. The patient is often discouraged and copes suboptimally with his diagnosis and the aggressive treatment (Fig. 22.1).

Adolescence is commonly defined as the age range between 11 and 20 years, 12 and 19 years, or 13 and 25 years. Others define adolescence as a stage between childhood and adulthood, or as an overlap of both childhood and adulthood (Fig. 22.2). Adolescence has been described as a period of life characterized by “storm and strife”, rebellious behavior, and disagreement with parents and other authority figures [24]. Adolescence entails a process of growth and development when the healthy individual gains more control and independence [25].

22.2.1.1 Cancer and Adolescence

Cancer is very often the first personal encounter of the adolescent with death. The diagnosis of cancer and its treatment cause loss of control and increased dependency, when parents and physicians tend to protect the patient from facing the risks of morbidity and mortality. This situation may interfere with normal psychological development during adolescence.

The unclear line of responsibilities regarding the administration of drugs in the adolescent age group affects drug compliance [8, 26]. Parents of adolescents tend to be too optimistic regarding the compliance of their adolescent children with oral chemotherapy [27]. Adolescents have been described both as “abusers of nonprescribed drugs” and as “nonusers of prescribed drugs.” Scare techniques also have been found to be rarely effective [28].

22.3 Assessment of Compliance

Identification of noncompliance is important in explaining the absence of a therapeutic response, targeting individuals for intensive intervention, and the selection of appropriate compliance-improving strategies. Unfortunately, poor compliance is difficult to anticipate because of the lack of clear factors that predict which children will be compliant. Moreover, this assessment must include parents and other family members, which may complicate the process. Once lack of drug compliance is suspected, factors associated with noncompliance or patients at risk for noncompliance should be identified and targeted for intervention.

Both indirect and direct methods have been used to identify and monitor patients' compliance (Table 22.1), with advantages and shortcomings for each technique. Measurement of compliance over a short period of time may not reflect long-term patterns [29] and methods used for research purposes may not be practical for routine clinical use. An individualized approach should be chosen for each patient according to the conditions, personality of the patient, and the health-care providers. A combination of different techniques, particularly direct and indirect methods, might be

particularly useful. Compliance studies using patients' and parents' questionnaires have demonstrated a rather high correlation with objectively measured compliance [30]. In adolescents with cancer, a strong correlation was found between subjectively reported compliance and the blood levels of medication [9].

22.3.1 Indirect Methods

Reports from patients and parents as to whether drugs are being administered are a valuable and practical way to get a first impression in clinical practice. Questioning patients per se tends to increase adherence by serving as a reminder to take the medication [31]. Therefore, interviews on drug compliance may serve as an effective intervention [9]. Self-reports of noncompliance are often more accurate than self-reports of compliance [32]. The questions used in such investigations should be nonthreatening and nonjudgmental.

Written reports, diaries, and questionnaires, in which patients or family members record drug intake, may be helpful in obtaining more accurate data from the patient in order to monitor drug compliance.

Pill counts may document a discrepancy between the number prescribed and/or reported to be taken and the number of remaining pills. The value of this method may be limited in clinical practice, because patients may not always bring their medications to the clinic visit and drugs could have been vomited, spilled, or spit out [31]. In addition, patients may intentionally discard unused medications; this is known as the "parking-lot effect," or "pill dumping effect" [33].

Physicians tend to overestimate drug compliance [34]. Noncompliance is often suspected with treatment

failure, but clinical outcome or absence of side effects cannot be used as reliable indications of noncompliance, since the disease does not always respond to the treatment [6] and side effects do not always correlate with drug intake.

22.3.2 Direct Methods

When noncompliance is suspected on clinical grounds, direct methods to assess compliance may be useful. These include measurement of drug levels in the blood or urine [11] and specific tracers added to the drug for better monitoring [31]. However, this information typically reflects only recent ingestion of the drug and patients may alter their compliance just prior to the test [35].

The leukocyte count may serve as a surrogate marker for the oral intake of 6-mercaptopurine, as may the clinical and hematological side effects of steroids. Yet there is not necessarily a linear correlation between the clinical or laboratory effects and the amount of drug ingested.

Recently, various microelectronic automated devices such as the Medication Event Monitoring System (MEMS, Apres Corporation, Fremont, California) offer a major advantage to monitor compliance [36, 37], particularly in noncooperative patients [38]. Microprocessors in the cap of these standard drug containers record every bottle opening as a presumptive dose. MEMS can monitor compliance over a period of time. For the individual patient, MEMS may help to determine the pattern of noncompliance and differentiate between poor compliance and pharmacodynamic or pharmacokinetic mechanisms leading to

Table 22.1 Indirect and direct methods to assess patient compliance (after Matsui [39]). *MEMS* Medication Event Monitoring System

Indirect methods	Direct methods
Patient and parental report	Measurement of drug levels in blood/urine
Interview, questionnaires	Measurements of tracers added to drugs
Pill count	Surrogate markers for drug intake (e.g., leukocyte count)
Physician's estimate	Automated devices (MEMS)
Clinical outcome	

low drug levels [39]. The use of electronic compliance monitoring has resulted in the recognition of different patterns of drug noncompliance, which can then be addressed better by the physician. For instance, the compliance with the evening dose tends to be higher than with the morning dose, possibly due to more intensive parental supervision in the evening than in the busy hours of the morning. Dose omissions are the most common dosing errors [40], and include incorrect dosage, premature discontinuation of the drug, and failure to fill the prescription, which was found in 5 to 20% of cases [41]. Studies with MEMS showed the pattern of “drug holidays,” defined as a period of 3 or more drug-free days, often during holidays or weekends [42]. An improvement in compliance several days prior to a scheduled medical visit has been observed and has been called the “toothbrush effect” or “white-coat compliance” [35, 43]. The data obtained from parents and patients can be studied systematically with

MEMS and the results of drug dosing patterns of non-compliant children would be useful in designing a more appropriate medication regimen for those children. The expense and the incorrect use of electronic monitoring devices are major drawbacks for a broad clinical use of MEMS [6]. Less expensive electronic compliance monitors would be more practical for widespread use, particularly in noncompliant adolescents with cancer.

22.3.3 Risk Factors and Predictors of Noncompliance

A variety of factors may influence patient’s compliance (Table 22.2): (A) the disease and its treatment, (B) demographic and social factors, and (C) the child’s and the parents’ knowledge and attitudes toward the disease and its treatment. Clinically, these factors might be important indices of suspicion, but they are

Table 22.2 Factors predicting drug compliance (modified from Tebbi 1993 [8])

A. Features of treatment and adverse effects of medication	<ul style="list-style-type: none"> Duration of treatment Physical characteristics of medication Number of medications Number of doses each administration Mode of administration Administered by healthcare provider vs. self-administered drugs Cost Number, severity, and expectations of side effects Appearance (color, taste, and size) of the tablets
B. Demographic and social factors	<ul style="list-style-type: none"> Age and sex of child Family socioeconomic status Marital status of mother Parent of child responsible for medication Parent accompanies child to provider Effect of child’s illness on family life
C. Child’s and parents’ knowledge and attitudes	<ul style="list-style-type: none"> Purpose of medication Dosage Frequency To-do list No overflow of information regarding long-term (“U-shaped” correlation) Belief about the effectiveness of the medication Beliefs about cancer cure Satisfaction with medical care received Control over health outcomes Instructions about medication given and understood Satisfaction with information about the disease and treatment

not reliable as predictors of the patient's drug compliance [44].

22.3.3.1 Features of Treatment and Adverse Effects of Medication

The severity of the disease as assessed by physicians has not been found to correlate with compliance [22]. Compliance may be related to the duration of treatment, the physical characteristics of the drugs such as the number of these, the number of doses for each administration and the mode of administration. The cost, and the appearance, color, and size of tablets can all influence drug compliance. Palatability is a very critical factor in children [45, 46]. Compliance is higher with medications administered by a health-care provider when compared with self-administered drugs. Compliance decreases significantly over the duration of treatment when the treatment exceeds 5 days [2]. In a study of 46 children and adolescents with cancer and 40 of their parents, compliance, judged by response to questionnaires and by bioassays, was >80% at 2 weeks of therapy and decreased to 60% by 20 weeks [9]. Compliance is better with drugs having less or milder side effects and among patients whose expectations about side effects were worse or about the same as what actually occurred. However, others have found no correlation between side effects and compliance [9]. In some studies compliance may be decreased by complex regimens, prolonged therapies [47], oral self-administered medication and regimens causing severe side effects. Compliance tends to decrease sharply soon after the child's symptoms have improved and is generally lower in the treatment of asymptomatic conditions or with preventive medications [48].

22.3.3.2 Demographic and Social Factors

The studies analyzing the correlation of compliance with demographic and social factors have been controversial and did not demonstrate any evident relationship [22]. Patients aged about 10 years of age tend to be good compliers, as opposed to very poor compliance at the age of about 17 years. The child's illness has an effect on the life of the whole family; strong family cohesiveness, positive attitudes of others, and avail-

ability of help and support by the family enhance compliance [49–51], whereas family dysfunction may be a risk factor for noncompliance [22]. The socioeconomic status of the family per se does not necessarily correlate with compliance. The compliance of children of single parents or of children coming without company to the clinic visits tends to be reduced [52].

22.3.3.3 Parents' and Child's Knowledge and Attitudes

The child's understanding of the disease has a major impact on compliance. The interaction and communication with the health-care provider are crucial. Educational conversations shortly after diagnosis are often not very effective due to the emotional trauma at that time. Misunderstanding and forgetting are aggravated by stress, and during the visit to the physician up to 50% of advice and instructions are forgotten almost immediately [53]. Only 50% of instructions given by physicians are recalled immediately following the visit [32]. Therefore, repeated discussions with the health-care providers, a written contract, and a home-support person to clarify the responsibility of drug administration tend to enhance compliance. Positive effects on compliance were found if the health-care provider relates in a friendly and respectful way to the patient, shows interest in the child [54], and believes in the efficacy of the treatment [55]. Better compliance is correlated with more visits to the physician, with patients attending specialized and private clinics, probably due to individualized attention [56], and better understanding of instructions. Defining with the parents the responsibility for drug administration improves compliance [9, 57].

The nature of the knowledge of the disease is critical: Practical knowledge about the purpose of the treatment, and dosage and frequency of drug intakes enhances compliance, whereas an overload of information extending beyond the practical aspects of the regimen like lifelong consequences, side effects, and prognosis, may result in discouragement and futility, and therefore in a "U-shaped" correlation with compliance [58]. The attitude and the belief system [59] of the patient may correlate with good compliance and outcome [16].

22.4 Discussion

Noncompliance with therapy is widespread among adolescents with cancer, who are at particularly high risk, since their malignancies may have a poorer prognosis than those of younger children and the state of mind of the adolescent may interfere significantly with adherence to treatment. Therefore, the importance of compliance in adolescents with cancer cannot be overemphasized.

In order to develop with the family and the health-care team an individualized approach for each patient, we suggest a checklist for the physician (Table 22.3). Continuous educational efforts and reinforcement should be tailored to meet the needs of the individual patient during various stages of the disease and intervening social and medical changes. It is through proper education and personalized needs assessment and intervention that progress toward better compliance can be made [8].

Communication skills are crucial to identify and to address noncompliance. Only few patients object when

a compliance measurement is proposed and its rationale explained [60]. Treatment goals should be discussed in collaboration with the patient and his family. Explicit instructions should be provided. The prescribed regimen should be simple and tailored to the patient's daily routine. Written information including educational handouts, self-monitoring calendar, schedules ("road maps"), and brief telephone reminders might improve communication [61].

A positive, hopeful, and encouraging attitude will improve compliance as part of the relationship between the physician and his patient. A careful review of the risk factors listed above may guide clinicians to identify problems. For noncompliant patients, different measures might be appropriate: More frequent visits for follow-up, social support, monitoring drug levels in blood or urine, replacing oral self-administered medication with parenteral medication, and finally, using sophisticated electronic pill containers. Favorable results using behavioral strategies, such as self-monitoring, contracting, and reinforcement programs, have been obtained with chronic disease treatment regimens [22].

Table 22.3 Suggestions to improve compliance. *PPR* Patient-physician relationship

1. Think about the compliance of each of your patients.
2. Address compliance with your patient and his family and listen to them very carefully.
3. Regularly report issues of compliance in the patient's chart, including the attitude of the family and friends.
4. Discuss compliance with your team of health providers.
5. Reduce forgetfulness and misunderstanding of your explanation with detailed written information including schedules ("road maps"), calendars, and other reminders.
6. Involve the patient and his family to share and define responsibility. Questionnaires and personal charts for the patient may be very helpful.
7. Check Table 22.2 and consider individual improvements.
8. A positive and hopeful attitude with encouragement will enhance compliance and well being of the patient and his family.
9. For noncompliant patients consider
 - [i] More frequent visits for follow-up
 - [ii] Provide immediate and extended family and social support
 - [iii] Monitor drug levels in blood and urine
 - [iv] Replacing oral self-administered medication by parenteral medication
 - [v] The use of sophisticated electronic pill boxes
10. Assess your own skills to address issues of compliance. Try to improve your PPR. Feedback of your skills!

Patients' adherence to physicians' instructions depends very much on the interpersonal skills of the physician and her/his ability to understand the patient's personality and needs. The complexity of compliance leads to reflections on the mission of the physician, defined as the holistic management of the patient and on the PPR. As suggested by Emanuel and Emanuel [62], there are different models for the PPR in the adult population (Table 22.4). The relationship may differ significantly in various clinical situations for which different models may be appropriate. Historically, there has been a shift in the PPR from paternalism to increased autonomy of the patient. The principle of "autonomy" has a different role in these four models, increasing from left to the right. Similar shifts have occurred in nonmedical professions such as politics, education, religion, and law. The ideal modern model of PPR is the deliberative model, in which the physician is a teacher and friend of the patient, and the dialogue deals with the worthiness of health-related val-

ues. The patient's autonomy is a moral self-development, supported by the physician's values, which are relevant to the patient. Particularly for a longstanding relationship during cancer treatment, the deliberative model of PPR seems to be most appropriate [63].

The four models of PPR for adults of Emanuel and Emanuel [62] have to be modified for pediatric patients and their families. The autonomy of the child is limited by definition, but is certainly not absent. In adolescent cancer patients, all of these models may apply simultaneously. Over the longstanding treatment of cancer, the adolescent patient may actually mature and undergo a development through all four models of the PPR. His individual psychological maturation parallels the historical development of the four models. From a very minimal role in the paternalistic model, the autonomy according to the informative model expects the patient to accept the technical facts and the professional expertise of the physician. According to the interpretative model, the autonomy of the patient

Table 22.4 Four models of the PPR (after Emanuel and Emanuel 1992) [62]

Conflict between autonomy (patient) <-> paternalism, health (physician)				
Model	Paternalistic	Informative (scientific, "engineering")	Interpretative	Deliberative
Role of Physician (Paternalism, Health)	Guardian of health, dictates to the patient	Provides facts, technical expert	Provides facts, technical expert -> Interpret and elicit patient's values "counselor"	Teacher/friend Dialogue on the worthiness of health-related values
Role of patient (autonomy)	Minimal function	Autonomy = values fixed	Autonomy = Self-understanding	Autonomy = moral self-development
Comments	"Patient control"; justified only in emergency situation	Lack of care and understanding the patient, no self-reflection and deliberation; based on trend of specialization and impersonalization of medicine, physician is a technologist. Justified in walk-in-clinic, consultations	Place for "second-order desires", particularly if conflicting values in patient present and ongoing relationship Physician's values unwittingly imposed upon the patient (shift to paternalism)	Ideal concept of autonomy; physician's role for patient; physician's values are relevant to the patient Patient's and physician's values are incommensurable

means self-understanding of his disease [64], whereas in the deliberative model the autonomy is a moral self-development during the dialogue with the physician.

It is evident that the PPR plays a crucial role in drug compliance for adolescent patients with cancer. During the longstanding treatment of the patient with cancer, a mutual trust is essential to ensure cooperation and compliance.

The quality of the PPR influences adherence with therapy, showing better results with patients who were treated consistently by the same physician than patients treated by different physicians on different occasions [47]. Adherence is usually better with patients treated by pediatricians in private practice than by pediatricians in a hospital setting [28]. Understanding the parents' major concerns and meeting their expectations from the medical visit during the prolonged time of active treatment and follow-up are extremely important for successful compliance [65]. Therefore, the physician should develop his/her skills toward a longstanding dialogue with cancer patients and their families. Continuous educational effort from both patients with their families and the health-care team are necessary [66].

The essential role of compliance needs more attention in order to prevent therapeutic failures. Most of the research on compliance has been conducted in the adult population, and these issues are not yet well studied in pediatrics. There is a need to improve education of the patient and his health-care providers with respect to compliance.

The training of all physicians, and particularly of oncologists, should address the importance of compliance. Input from clinical psychology and communication skills are crucial to improve the PPR, particularly in chronic diseases. Physicians caring for children should be educated to have a high index of suspicion for drug noncompliance. Identification of potential barriers to compliance may allow for early intervention to ensure compliance and minimize the negative consequences of inappropriate administration of medications.

Compliance remains a poorly understood subject and a source of frustration for today's practitioners. Clinical research to identify noncompliers and to treat them optimally is crucial. Research on compliance

does not only address the patient and his psychology, but also has a major impact on drug development and treatment regimens [60]. Moreover, the attitudes to better understand and address noncompliance may improve the well being of the patient and the overall quality of the PPR.

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