

Thomas Klauer
Uwe K. Zettl

Compliance, adherence, and the treatment of multiple sclerosis

■ **Abstract** With the availability of disease-modifying, immunomodulatory

Dr. T. Klauer (✉)
Medizinische Fakultät der Universität
Rostock
Klinik und Poliklinik für Psychosomatik
und Psychotherapeutische Medizin
Gehlsheimer Str. 20
18147 Rostock, Germany
E-Mail: thomas.klauer@med.uni-rostock.de

Prof. Dr. U. K. Zettl
Medizinische Fakultät der Universität
Rostock
Klinik und Poliklinik für Neurologie
Gehlsheimer Str. 20
18147 Rostock, Germany

therapies (DMT) for multiple sclerosis (MS) and the first long-term studies, it became obvious that problems of compliance to complex treatment regimens under chronic conditions would also apply to these approaches. In a selective overview, problems and findings of adherence research are depicted. Based on a discussion of basic concepts, issues of operationally defining and measuring adherence are outlined. Descriptive findings on adherence to DMTs and empirical predictors of nonadher-

ence are then discussed. Referring to theoretical models of treatment motivation, selected problems (e.g., indication) and strategies of promoting adherence are described. Finally, implications of modern concepts of the patient-therapist relationship for the issue of patient adherence are considered.

■ **Key words** multiple sclerosis · compliance · adherence · immunomodulatory treatment · counseling

Introduction

Even highly potent medical treatments may be limited in their effectiveness by the degree to which patients continue to exactly follow the treatment procedure (e.g., medication) over the entire treatment course (compliance). Recently, the term “adherence” has been preferred over the concept of compliance because of the authoritative and paternalistic connotations of the latter. Adherence has been defined as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” ([30], p. 3). Frequently, more specific aspects of adherence like persistence (i.e., the time interval between the first application of a medicament and withdrawal from continuous application contrary to the health care provider’s recommendation) and performance quality (i.e., stability regarding dosation scheme and mode of application) are further distinguished [4].

Nonadherence is usually seen as an unnecessary risk

for further morbidity and mortality and as a waste of health care resources. Nevertheless, it is a frequent phenomenon with proportions from 12 % (HIV disease) up to 33 % (diabetes) of nonadherent patients in various diagnostic groups with an average nonadherence rate of nearly 25 % [6]. This estimate from a meta-analysis is similar to findings on adherence to immunomodulatory treatment (disease-modifying therapy, DMT) of multiple sclerosis (MS). According to a recent review [12], empirically observed nonadherence rates in DMTs vary between 6 % and 43 %. Differences in definitions and measures of adherence considerably contribute to these variations.

Definition and assessment of (non-)adherence

Adherent behavior may constitute a difficult task for patients especially in chronic and complex conditions. According to Meichenbaum and Turk [14], this task comprises six domains of behavior, i.e., (1) utilization and consequent maintenance of therapy, (2) to keep treat-

JON 6016

ment and aftercare appointments, (3) to take drugs correctly, (4) to actively change health lifestyles, (5) to do treatment-related “homework” and (6) to reduce risk behaviors (e.g., smoking).

The more complex the task of treatment adherence presents for patients, the more difficult it is to distinguish nonadherence from incomplete adherence. For research purposes, operationally defined criteria have been introduced (e.g., taking correctly 80 % of the medication or more; 33 % missed applications over one month [19, 28]). When comparing different medication schedules and preparations (e.g., in the immunomodulatory treatment of MS; [29]), operational standard measures of adherence also have to be developed.

In contrast to complete adherence, nonadherent behavior is a manifold phenomenon. Major types of nonadherence are (1) complete refusal of therapy, (2) refusal of specific treatment options and (3) arbitrary or unintended modification of prescriptions. Moreover, several subtypes can be distinguished which include intentional clandestine (“covert”) noncompliance, but also supplementation of medication by commercially available drugs as well as drug intake without an indication (“hypercompliance”; [19]).

A number of instruments has been developed to assess adherence, which are usually divided into the categories of direct and indirect measures. The most frequently applied and, at the same time, most unreliable assessment approach, i.e., the patient self-report, is subsumed among the *indirect approaches* in which adherence is inferred from indicator variables. Even when compared to other indirect measures like, e.g., pill counts, prescriptions and pharmacy files, patients (as well as their physicians) tend to overestimate adherence so much that this procedure is widely seen as inappropriate. Among the indirect measures, electronic registration of medication consumption by *Medical Event Mon-*

itoring systems (e.g., electronic pill-boxes) are preferred especially in naturalistic studies and have been developed for a wide range of medication modalities in internal medicine, neurology, and ophthalmology.

In clinical studies, *direct measures* of adherence are indispensable in which medication intake is assessed in an unmediated way. This is accomplished either by direct surveillance of intake, which can only rarely be realized in practical care, or by verification of the active agent or its metabolites, but also of marker substances in the blood or urine. These approaches require sensitive biochemical detection methods in order to avoid false negative findings.

Adherence to immunomodulatory treatment of MS

Immunomodulators like interferon beta (IFN β -) 1a, IFN β -1b, and glatiramer acetate are central components of MS platform therapy which should reduce the development of new lesions in the central nervous system, the frequency of exacerbations, and both physical and cognitive impairment. The most severe demand that immunomodulatory treatment imposes upon patients is that it involves medication that must be injected highly frequent (every day, every other day, or once a week) over an extended period of time (months or even years) subcutaneously or intramuscularly. Benefits of DMTs will not be positively experienced by the patients, but should appear as reduced frequency of exacerbations. Instead, flu-like side effects including flushing, chest pain, palpitations and dyspnea are frequent and challenge the patient's adherence.

In empirical studies of DMT adherence (Table 1), these side-effects and perceived lack of treatment efficacy were most frequently mentioned as reasons for discontinuation by patients [12]. As in adherence studies in

Table 1 Adherence to immunomodulatory treatment of MS in selected studies

Study	Year	Sample size	Course of MS	Type of study	Time frame	Nonadherence %	Remarks
Mohr et al. [17]	2001	101	RR	Prospective, telephone report	6 months	12.9	Trained patients
Milanese et al. [15]	2003	1481	RR	Prospective	3 years	15.3 – 41.1	
Ruggieri et al. [23]	2003	122	RR	Prospective	5 years	39.3	
Tremlett & Oger [28]	2003	844	RR	Retrospective, hospital charts	6 months	27	
Fraser et al. [8]	2004	108	RR, SP	Prospective	6 months	21.2	
Haas & Firzlaff [9]	2005	308	RR	Prospective	2 years	30.2	
O'Rourke & Hutchinson [18]	2005	394	RR, SP	Retrospective, hospital charts	3 years	14 (RRMS) 23 (SPMS)	
Rio et al. [22]	2005	622	RR, SP	Retrospective	Md = 47 months	13.5 (RRMS) 30 (SPMS)	Trained patients
Turner et al. [29]	2007	90	n.a.	Prospective	6 months	12.9	
Portaccio et al. [20]	2008	225	RR	Retrospective	M = 4.2 years	45.8	Switchers included

M mean; Md median; RR relapse-remitting; SP secondary-progressive

other diagnostic groups, proportions of nonadherent patients vary within a broad range between nearly 13 and nearly 46% of patients, depending on type of study, follow-up interval, definition of nonadherence, course of MS, and immunomodulators. Results from pivotal clinical studies (which are not considered here) mostly yielded results below this range.

While differences between the various immunomodulators are not consistent and confounded with type of study, adherence seems to be higher in patients with relapse-remitting (RR) than with secondary-progressive (SP) course [18,22]. Most drop-outs seem to occur within the first two years of treatment [12]. Most studies converge in that the risk of nonadherence grows with higher extended disability scale scores (EDSS). Moreover, non-adherence rates are higher in studies from clinical practice as compared to large-scale prospective studies.

Besides selection biases, a reason for this observation might be that in clinical practice switches between immunomodulatory drugs are common [18] and may have been erroneously categorized as cases of nonadherent behavior in some studies. Differences between studies may also result from differences in the amount of training and information patients had received before entering immunomodulatory treatment (e.g., [17]).

Determinants of adherence

Missing treatment effects or undesirable side effects empirically explain only medium amounts of variance in adherence. Besides characteristics of treatment, (1) disease characteristics, (2) patient variables, (3) quality of the patient-therapist relationship, (4) treatment setting and (5) influences from the social environment can be distinguished as important determinants of adherent behavior [19].

Among patient characteristics, informational deficits, motivational deficits, and psychological disorders have most frequently been discussed. Obviously, adherence is most strongly threatened by disorders that specifically and directly interfere with medication application like, e.g. injection phobia in the immunomodulatory treatment of multiple sclerosis [17] or treatment of diabetes. Depression represents a more general risk to adherent behavior.

Informational deficits in the patients which can lead to problems like, e.g., instable intake contingencies, have long been regarded as a result of an inaccurate patient-physician communication. In many areas of medicine, attempts have been undertaken to optimize communication and to place it on a more cooperative foundation (e.g., shared decision-making; [10]). In psychological approaches to subjective theories of illness [13], it is assumed that uncommunicated, dissenting lay concepts of patients lead to a selective encoding of illness-related in-

formation and to biased information processing. Subsequently, patients might avoid confronting therapists with their diverging ideas. In this process of developing nonadherence, risks of abandoning intake are frequently underestimated.

Psychological models of adherence mostly refer to motivational factors like degree of suffering, lay etiology or treatment expectations [24]. Usually, it is assumed that higher levels of suffering and more positive expectations regarding treatment effectiveness should go along with greater adherence. However, the concept of treatment expectations is multidimensional: subjective probabilities of desired and undesired consequences of adherent and nonadherent behavior should similarly determine compliance to somatic as well as psychological treatment; these probabilities have been systematically described within expectancy-values approaches (e.g., [19]).

One of the first theoretical accounts for compliant behavior was the Health Beliefs Model (HBM; [1]). According to the HBM, the individual tendency to engage in preventive health behaviors as well as compliant behaviors under treatment is influenced by four types of expectations: (1) the perceived severity of an illness, (2) the perceived vulnerability to that illness, (3) the perceived benefits expected from a specific health behavior and (4) the perceived barriers to engage in a specific health behavior. Recently, the HBM has been applied to immunomodulatory treatment of MS [29] using one of the three beta interferon (IFN β) preparations or glatiramer acetate. Treatment adherence as well as satisfaction at the 2-, 4-, and 6-month follow-ups were consistently predicted only by perceived benefits but not by the other model variables. However, expectations regarding treatment outcomes may also be unrealistically positive, and patients holding them are at risk to discontinue treatment because of frustration and disappointment.

Since treatment adherence over longer periods of time has turned out to be a dynamic and probably unstable phenomenon, process or stage models of health behavior change have also been proposed to explain interindividual differences. In the Transtheoretical Model (TTM) of health behavior change [21] it is assumed that patients pass through a progressive sequence of stages of readiness for change. As defined in the model, these stages include (1) precontemplation (i.e., not thinking about changing behavior in the next six months), (2) contemplation (thinking about changing the behavior in the next six months but not in the next 30 days), (3) preparation (ready to change in the next 30 days), (4) action (changed fewer than six months ago) and (5) maintenance (changed the behavior more than six months ago). Since empirical tests of the model challenged distinctiveness of the stages as well as unidirectionality of the change process [7], criteria were reformulated less

restrictively, and additional variables were integrated like, e.g., "pros" and "cons" of changing as well as perceived barriers. The TTM has been applied to the discontinuation of immunomodulatory treatment of MS with IFN β -1a and was found to correctly identify 82 % of the nonadherent and 81 % of the adherent patients together with level of education and disability as predictors [2].

Self-efficacy is another type of expectancy that has been frequently shown to predict a wide range health behaviors [25]. It is defined as the subjective probability to be able to perform a health-related behavior or, more specifically, concrete action in support of medical treatment. Self-efficacy expectations should be especially relevant in the "post-intentional" phase of treatment motivation when compliant behavior has to be maintained in the face of barriers and obstacles like, e.g., negative side effects [26]. Mohr et al. [17] found self-injection self-efficacy before and during IFN β -1a therapy to predict treatment adherence after six months. In a prospective study on glatiramer acetate [8], adherent and nonadherent patients significantly differed on the Multiple Sclerosis Self-Efficacy Scale (MSSE; [27]).

A comprehensive model of treatment adherence should not only integrate patient, therapist, illness and treatment factors but also exogenous influences especially from the social environment. Social support from spouses and friends may contribute much to the adherent behavior of the patients: According to meta-analytic results [5], patients lacking instrumental social support (e.g., material aid, assistance in practical problem-solving) bear a 3.6-fold higher risk of nonadherence. Thus, it might be useful to include patients' relatives in adherence-related interventions.

Interventions to promote adherence

Because determinants of nonadherence are manifold and heterogeneous, patients at risk should undergo detailed assessment along the above mentioned categories of variables to ensure that adequate strategies of compliance promotion are assigned. For example, patient education focusing on illness-related information should not be appropriate to resolve motivational deficits which interfere with regular intake of medication. Following the identification of patients at risk by certain key features (e.g., negative experiences with similar treatments; difficult social environment; [19]), a diagnostic sequence assessing deficits in illness-related knowledge (indication for information), deficits in practical skills (indication for education) and, finally, motivational deficits (indication for motivational intervention) has been suggested [11]. More specific diagnostic procedures may then be used to identify target variables for intervention in individual patients (e.g., unrealistic treatment expectations).

While MS patients are often well equipped with information and skills (e.g., by self-injection training), only few motivational interventions have been proposed for this group. To enhance treatment motivation and adherence, interventions have to be tailored to the specific deficits of the patients and to consider the more general aims and incentives patients are committed to in their lives as well as the stage of change patients are actually in. Group intervention approaches to promote adherence, thus, should be designed flexible as well as comprehensive and involve informational, behavioral, and motivational components.

An initial aim of such interventions is to encourage patients to take responsibility for their treatment. For example, self-commitment to change is a central concept of *motivational interviewing* (MI), a counseling strategy which has been transferred from addiction therapy to many other areas of medicine and clinical psychology [16]. Basic principles of MI are cooperation, activation of intrinsic motivation, and autonomy. These principles are reflected in an empathetic style of counseling, active listening, abandonment of reasoning to avoid patient resistance and addressing the patients' ambivalence regarding treatment continuation. Specific strategies of MI are, e.g., enhancement of problem recognition, the promotion of self-efficacy, and the configuration of change plans with respect to time criteria. Some specific aspects of MI were integrated into a software-based telephone counseling intervention [3]; in a study with 366 patients, it could be shown that adherence to IFN β treatment was remarkably higher in the intervention group (98.8%) compared to standard care controls (91.3%).

Conclusions

In many cases, treatment of chronic disease challenges the patients' self-management skills and motivational resources by demanding medication intake, following a diet, and changing the individual lifestyle. This applies also to standard immunomodulatory therapies of multiple sclerosis which require the careful maintenance of (self-)injection schedules and, sometimes, the tolerance of undesired side effects. As in other chronic conditions, a substantial proportion of patients does not adhere to treatment at least for some time.

Nonadherence rates reported from studies with MS patients vary within a broad range between nearly 13 and nearly 46 % of patients, depending on type of study, follow-up interval, definition of nonadherence, course of MS, and immunomodulators. Current evidence indicates that a progressive course of MS, higher disability, lower self-efficacy, lower motivation to change, and lower perceived benefits predict nonadherence to DMTs in multiple sclerosis. One of the few studies on adher-

ence interventions in MS patients showed that telephone-based counseling using a motivational interviewing strategy contributed to a reduction of discontinuation rates. Nevertheless, nonadherence remains a serious problem in the treatment of MS.

Usually, nonadherence is regarded as a risk for patient morbidity and mortality and as an unnecessary economical burden for the health care system. Nonadherent behavior has mostly been attributed to *deficits* in cognitive or motivational characteristics of the patient, in the patient-therapist communication, in the treatment setting or in the social support networks of the patients. However, in modern reformulations of the patient-therapist relationship preferring strategies like empowerment and shared decision-making, the concept of nonadherence has also undergone a change of meaning [10]: From the perspective of the *expert patient*, who

is well informed about the limitations of treatment effectiveness, nonadherent behavior may well be the result of critical reflection of treatment options against the background of more general aspirations and aims in life. The heterogeneity of variations of (post-)intentional nonadherence suggests that the simple dichotomy of adherent and nonadherent patients might be too simple and not helpful in modern health care. Open communication between patients and health-care providers as well as shared decision-making should help to “uncover” intentional nonadherence of the clandestine type and, thus, to make the treatment process more efficient with regard to medical and economical outcomes.

■ **Conflict of interest** The authors have no conflict of interest to declare.

References

1. Becker MH (1974) The health-belief model and personal health behavior. Charles B. Slack, Thorofare
2. Berger BA, Hudmon KS, Liang H (2004) Predicting treatment discontinuation among patients with multiple sclerosis: Application of the transtheoretical model of change. *J Am Pharm Assoc* 44:445–454
3. Berger BA, Liang H, Hudmon KS (2005) Evaluation of software-based telephone counseling to enhance medication persistency among patients with multiple sclerosis. *J Am Pharm Assoc* 45:466–472
4. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK (2008) Medication compliance and adherence. *Value in Health* 11:44–47
5. DiMatteo MR (2004) Social support and patient adherence to medical treatment: A meta-analysis. *Health Psychol* 23:207–217
6. DiMatteo MR (2004) Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Med Care* 42:200–209
7. Drieschner KH, Lammers SMM, van der Staak CPF (2004) Treatment motivation: An attempt for clarification of an ambiguous concept. *Clin Psychol Rev* 23:1115–1137
8. Fraser C, Morgante L, Hadjimichael O, Vollmer T (2004) A prospective study of adherence to glatiramer acetate in individuals with multiple sclerosis. *J Neurosc Nurs* 36:120–129
9. Haas J, Firzlafl M (2005) Twenty-four month comparison of immunomodulatory treatments – a retrospective open label study in 308 RRMS patients treated with beta interferons or glatiramer acetate. *Eur J Neurol* 12:425–431
10. Heesen C, Berger B, Hamann J, Kasper J (2006) Empowerment, Adhärenz, evidenzbasierte Patienteninformation und partizipative Entscheidungsfindung bei MS – Schlagworte oder Wegweiser? *Neurol Rehabil* 12:232–238
11. Kanfer FH, Reinecker H, Schmelzer D (1996) *Selbstmanagementtherapie* (2nd ed.) Springer, Berlin
12. Kern S, Reichmann H, Ziemssen T (2008) Therapieadhärenz in der neurologischen Praxis. *Nervenarzt* 79:877–890
13. Leventhal H, Meyer D, Nerenz D (1980) The common sense representation of illness danger. In: Rachman S (ed) *Contributions to medical psychology* (vol. 2). Pergamon, New York, pp 7–30
14. Meichenbaum D, Turk DC (1987) *Facilitating treatment adherence: A practitioner's guidebook*. Plenum, New York
15. Milanese C, LaMantia L, Palombo R, et al (2003) A post-marketing study on interferon β 1b and 1a treatment in relapse-remitting multiple sclerosis: Different response in drop-outs and treated patients. *J Neurol Neurosurg Psychiatry* 74:1689–1692
16. Miller WR, Rollnick S (1991) *Motivational interviewing: Preparing people to change addictive behavior*. Guilford, New York
17. Mohr DC, Boudewyn AC, Likosky W, Levine E, Goodkin DE (2001) Injectable medication for the treatment of multiple sclerosis: The influence of self-efficacy expectations and injection anxiety on adherence and ability to self-inject. *Ann Behav Med* 23:125–132
18. O'Rourke KET, Hutchinson M (2005) Stopping beta-interferon therapy in multiple sclerosis: An analysis of stopping patterns. *Mult Scler* 11:46–50
19. Petermann F, Mühlig S (1998) Grundlagen und Möglichkeiten der Compliance-Verbesserung. In: Petermann F (ed) *Compliance und Selbstmanagement*. Hogrefe, Göttingen, pp 73–102
20. Portaccio E, Zipoli V, Siracusa G, Sorbi S, Amato MP (2008) Long-term adherence to interferon β therapy in relapse-remitting multiple sclerosis. *Eur Neurol* 59:131–135
21. Prohaska JO, DiClemente CC (1982) *Transtheoretical psychotherapy: Toward a more integrative model of change*. *Psychother Theory Res Pract* 19:276–288
22. Rio J, Porcel J, Téllez N, Sánchez-Betancourt A, Tintoré M, Arévalo MJ, Nos C, Montalban X (2005) Factors related with treatment adherence to interferon β and glatiramer acetate therapy in multiple sclerosis. *Mult Scler* 11:306–309
23. Ruggieri RM, Settiani N, Viviano L, Attanasio M, Giglia L, Almasio P, La Bella V, Piccoli F (2003) Long-term interferon-beta treatment for multiple sclerosis. *Neurol Sci* 24:361–364

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.