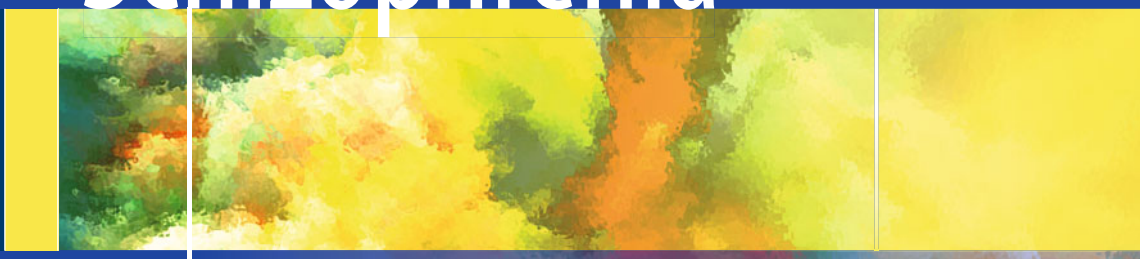
Adherence to Antipsychotics in Schizophrenia



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Preface

There is wide agreement that among the problems limiting the success of treatment for patients with serious mental illness, including schizophrenia, poor adherence to prescribed medication regimens is the most relevant and, at the same time, one of those potentially modifiable. Long-term adherence to antipsychotic therapy is the cornerstone of contemporary management of psychosis, since the consequences of non-adherence can be devastating for patients and their families in terms of personal suffering and reduced quality of life as well as for society in general, due to direct costs of healthcare and loss of income.

Despite the widespread nature and serious consequences of non-adherence to antipsychotic medications, there is evidence that physicians may not be aware when their patients discontinue their medications and that they overestimate their patients' adherence. Several factors concur to non-adherence, either related to the illness, to the patient, to the treatment, or to the therapeutic relationship, and some of them are partially or totally modifiable.

Increasing the awareness about factors affecting patient's non-adherence to treatment prescriptions and implementing the interventions that can improve medication adherence in patients with schizophrenia would be beneficial in maximizing treatment outcomes with antipsychotics.

Although numerous strategies have been proposed for improving adherence in patients with schizophrenia, including pharmacological, educational, and behavioral approaches, well-defined and generally accepted guidelines on the issue are not available and the need for a systematic review of the open questions related to adherence has been the main reason for planning and completing this volume. The book's start-point has been also the continuous collaboration between the authors involved and their common interest in the research and clinical management of adherence problems.

A definition of adherence, an overview of its diffusion and consequences, and of factors contributing to it are addressed in the first chapter of the book. The second chapter addresses the pharmacological strategies to enhance adherence in schizophrenia as well as the obstacles to it deriving from pharmacological treatment itself, while the third is devoted to psychosocial strategies to enhance adherence and continuity of care in schizophrenia. A final chapter analyzes in detail those psychological issues, involved in the patient−doctor relationship, able to improve therapeutic alliance.

The book addresses the different aspects of adherence in schizophrenia and related disorders in a systematic but easy-to-use textbook format. In such a format, the volume may be a part of educational programs devoted not only to psychiatrists but also to professionals working in psychiatric teams treating patients with schizophrenia and severe mental disorders. Also, researchers in the field of clinical psychopharmacology of psychoses, but also in that of long-term treatment of schizophrenia, of the outcome of severe mental disorders, as well as of integrated psychosocial strategies to enhance continuity of care and patient's outcomes could find useful information in the book for their work.

We hope that this book will prove to be of interest to physicians and professionals involved in the clinical management as well as in clinical research of severe mental disorders, especially schizophrenia. We do hope, also, that it could be of help for the patients themselves and their families, who suffer the major impact of non-adherence and poor outcome of the undertreated diseases.

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Abbreviations

AAI	Adult attachment interview
ACE	Adherence-coping education
ACT	Assertive community treatment
AT	Adherence therapy
CAT	Cognitive adaptation training
CBT	Cognitive-behavior therapy
CGI	Clinical global impression scale
CM	Case management
CPZ	Chlorpromazine
CT	Compliance therapy
DAI	Drug attitude inventory
DALYs	Disability adjusted life years
DSM	Diagnostic and statistical manual of mental disorders
ECA	Epidemiologic catchment area
EE	Expressed emotion
EMDR	Eye movement desensitization and reprocessing
EPPIC	Early psychosis prevention and intervention centre
EPS	Extrapyramidal symptom
EUFEST	European first-episode schizophrenia trial
FGA	First-generation antipsychotic
GAF	Global assessment of functioning scale
GES	Generic environmental supports
HBD	Health belief dialogue
HBM	Health belief model
HBQ	Health beliefs questionnaire
HR	Hazard ratio
ICD	International classification of diseases
ITAREPS	Information technology aided relapse prevention program
IWM	Internal working models
LAI	Long-acting injectable antipsychotic
LUNERS	Liverpool university neuroleptic side effect rating scale
Medi-Cal	California medicaid
MEMS	Medication events monitory system
MFG	Multifamily group therapy

MPR	Medication possession ratio
MUSE	Medication usage skills for effectiveness
NGA	New-generation antipsychotic
OR	Odds ratio
PANSS	Positive and negative syndrome scale
QUATRO	Quality of life following adherence therapy for people disabled by schizophrenia and their carers
RCT	Randomized controlled trial
RDC	Research diagnostic criteria
ROMI	Rating of medication Influences scale
RQ	Relationship questionnaire
SMS	Short message service
SOHO	Schizophrenia outpatient health outcomes
SWN	Subjective well-being under neuroleptic treatment scale
SWN-k	Subjective well-being under neuroleptic treatment scale, short version
TAT	Treatment adherence therapy
TAU	Treatment as usual
TIPS	Telephone intervention problem solving
TMM	Telephone medication management
US-SCAP	US schizophrenia care and assessment program
VA	Veteran affairs
VBP	Valued-based practice
VR	Virtual reality
VRAMMA	Virtual reality apartment medication management assessment
WAI	Working Alliance Inventory, short form
WHO	World Health Organization

Poor Adherence to Antipsychotic Medication in People with Schizophrenia: Diffusion, Consequences and Contributing Factors

Emilio Sacchetti and Antonio Vita

Premise

Even panacea does not work when the patient intentionally or unintentionally fails to take it. Once it is accepted that "the fate of a drug therapy is with the patient" [1], the inevitable consequence is that the patient is the ultimate health care decision maker. These common sense observations get even more complicated by factual evidence that the "ideal of the patient as a passive obedient recipient of medical instructions" [2] is far from the real world. Human kind is indeed generally reluctant to take medicines in the absence of adequate support.

The negative predisposition toward medicines has very old roots. More than 2000 years ago, for example, the conflicting nature of the man–drug ticket was popular, so that Titus Lucretius Carus [3] used it in an allegory to explain the stratagem of using poetry to disseminate the Epicurean lesson; in the fourth book of the *De Rerum Natura*, the poet–philosopher referred to the expedient of the

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physician who sweetens the rim of the glass with honey to induce the sick boy to drink the bitter absinth.

The presence of a disease may be not enough to motivate patients to follow the physician's prescriptions and dedicated incentives may be needed to induce correct use of medication, but it is also true that many proposed interventions are often unproductive in practice. For example, it was reported that, in a sample of healthy volunteers who were paid to take a daily single dose of aspirin and received explicit, written and verbal instruction to follow the prescription, only 35 % adherence was observed over a 2-week period [4]. Based on the various components of this discouraging sequela, it is far from surprising that poor adherence to medication regimens detracts relevant resources from the health care system and creates a heavy burden for the patients, the families and society. These dramatic consequences occur with all types of diseases and all types of medicines, even placebos. A meta-analysis of studies evaluating the association between adherence to drug therapy and mortality depicts the generality of the phenomenon [1]: compared with poorly adherent patients, those with good adherence presented lower mortality, irrespective of attribution to a beneficial drug or placebo. Considering the well-known tenet that placebo has little effect on health outcomes, it seems reasonable [1] that medication adherence is a proxy expression for a healthy adherer effect related to overall healthy behaviour.

Two examples demonstrate that major psychiatric disorders in general and psychoses in particular are privileged vehicles for poor healthy adherer effect, although with possible disorder-related specificities. The first is that compulsory treatments unrelated to quarantine constitute an almost exclusive prerogative of mental disorders. The second refers to the chronologic link that exists between the beginning of the psychopharmacologic era and the first explicit mention of medication non-compliance in a patient affected by a severe mental disorder. In a historical article from 1949 on the first series of 10 cases treated with lithium for psychotic excitement, John Cade [5] reported that a patient, a man with a "state of chronic manic excitement" recovered sufficiently on lithium to make return to "his old job" possible but developed a full-blown relapse leading to readmission to hospital once "he became more lackadaisical about his medicine and finally ceased taking it" even though he had received "instructions to take a maintenance dose of lithium carbonate, five grains twice a day".

Role of Antipsychotics in the Treatment of Schizophrenia

Nowadays, it is fully recognised that the best treatment option for people with schizophrenia requires multidisciplinary interventions. Nevertheless, it remains indisputable that antipsychotic drugs are the mainstay of therapeutic intervention. International guidelines on the treatment of schizophrenia, systematic reviews and meta-analyses [6–18] unequivocally lead to the same conclusion: although they are far from ideal as to efficacy and tolerability, antipsychotics, especially second-generation antipsychotics, play a vital role not only in the attenuation and

suppression of psychotic symptoms but also in the prevention of relapses and recurrences. The importance of continuous maintenance therapy with antipsychotics for a good long-term prognosis is also manifest after the first episode of schizophrenia. For example, first-episode patients have been reported to have relapses fivefold more frequently when antipsychotics are not taken as prescribed [19]. However, evidence-based conclusions probably do not present the best picture of pharmacotherapy on schizophrenia outcome. To get a more immediate idea on this issue, it may be for example remembered that individuals with psychosis experienced quite different results in the years immediately before and subsequent to the advent of chlorpromazine, the first of the neuroleptic medications [20, 21]. Previously, almost half of the patients admitted to psychiatric hospitals had to spend more than 10 years of their life in hospital [22]. When chlorpromazine became available, the number and length of the hospitalisations started to decrease enough to allow the transition, previously considered to be a largely utopian idea, from a model of care centred on the psychiatric hospital to a community-based approach. In addition, comparison of cohorts of patients evaluated in the same setting before and after the introduction of antipsychotic medications confirms how "the course of schizophrenia has become less malignant" concomitant with the advent of this class of agents, as indicated, in particular, by "the marked reduction in occurrence of catastrophic schizophrenia and virtual disappearance of catatonic schizophrenia over this timeframe" [23].

Although about half a century has elapsed since the first pioneering attempts at deinstitutionalisation, the valuable therapeutic potential of antipsychotic medications remains under-expressed for a significant number of patients. Successful pharmacotherapy for schizophrenia requires continuous consumption [24–28] but, in clinical practice, this requirement is far from being realised in a significant number of patients.

Schizophrenia has been reported [28] to rank second among the clinical conditions characterised by major difficulties in achieving levels of medication adherence sufficient enough to obtain a therapeutic effect, which attests to the presence of relevant obstacles to the use of antipsychotics.

Compliance Versus Adherence

The acknowledgement that patients frequently do not follow the prescriptions recommended by their doctors can be traced back to ancient times. However, the entry into medical terminology of the words compliance and adherence for this peculiar behaviour was relatively recent [29]. The authors of early pioneering reports on the effects of neuroleptics in the real world have systematically used circumlocutions such as "patients who do not take their drugs" [30], "patients who failed to take the drugs prescribed" [31] or patients who do not take the "courses of the drug prescribed as indicated by the doctor" [32]; the words compliance and adherence were not used to describe medication-taking behaviour.

Several definitions for compliance and adherence have been proposed over the years. However, all of them focus, with nuances, on "the extent to which a person's behaviour coincides with medical or health advice" [33]. The label embraces a wide spectrum of conditions such as, for example, "failure to enter a treatment program, premature termination of therapy, and incomplete implementation of instructions, including prescriptions" [34] along a continuum of distinct behaviours related to the amount and timing of medicines actually taken.

Compliance and adherence could also be considered according to a functional perspective as measures of health outcome, for example "the number of doses not taken or taken incorrectly that jeopardize the therapeutic outcome" [35] or "the point below which the desired preventive or desired therapeutic result is unlikely to be achieved" [36].

However, the definitions based on the extent to which a patient deviates from prescriptions from the health care provider or on the clinical consequences of a defined medication-taking behaviour do not get to the heart of the difference between compliance and adherence. The difference refers principally on two distinct models of the patient–doctor relationship. In particular, treatment and medication compliance are the expressions of a process of care centred on an indisputable leading actor, the paternalistic doctor who prescribes or, better, orders the therapy for a supporting actor, the patient, without paying appreciable attention to an alliance. Treatment and medication adherence are the expressions of a process of care centred on two principals, the doctor and the patient who are actively engaged in genuinely shared decisions within their specific roles. Therefore, the gap between compliance and adherence is not trivial and not confined to mere semantics but has relevant implications for clinical practice. Despite this, many publications incorrectly use compliance and adherence as synonyms.

The prevalence of one term or the other has fluctuated over time. The result of a MEDLINE search on articles from 1976 to 2011 citing compliance and/or adherence in schizophrenia (Fig. 1) testifies to how the initial preference for compliance has been progressively changed to a gain in popularity for adherence; nowadays the terms are used almost equally. The risk is that the current inclination to qualify the reduced propensity of patients to take medicines as adherence depends principally on its more politically correct profile rather than real evolution of patient–doctor communication.

Given the differences characterising the two labels, research on medication-taking behaviour should state whether a study refers to compliance or adherence. In this regard, an acceptable, easy option could consist of systematic reports on the

[1] Although compliance and adherence identify different degrees of participation of the patient within the care process, studies rarely state explicitly whether they are dealing with compliance or adherence by the patient. Therefore, the term chosen in this chapter is based on the specific label used in the individual articles being discussed. Adherence is used for general or personal considerations because this is the term preferred by the authors.

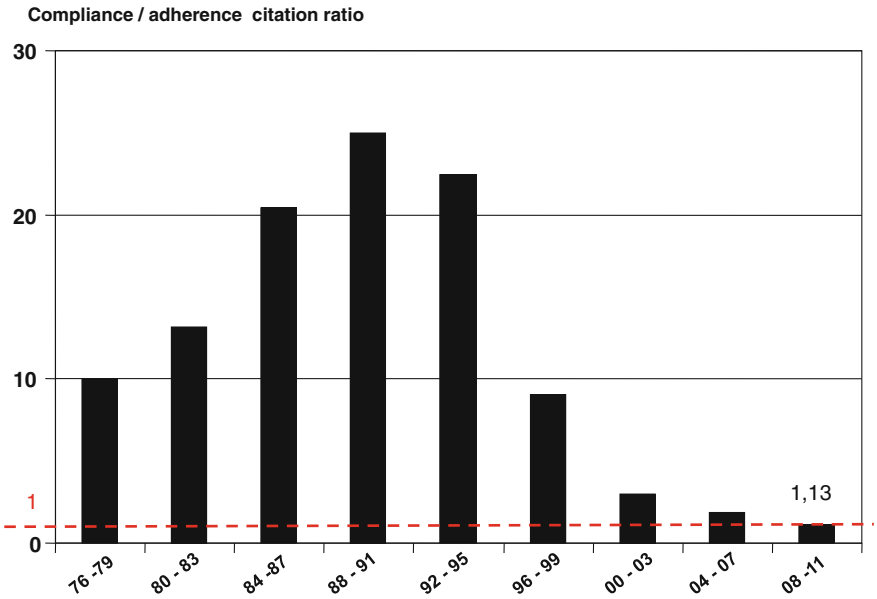

Fig. 1 Changes over the years of the MEDLINE compliance/adherence citation ratio in studies on schizophrenia

interventions used to promote active participation of the patients within the treatment project[1].

Assessment of Medication Adherence

Treatment adherence is a favourite topic in modern research on schizophrenia and related disorders. The growing interest of the scientific community in the topic is illustrated by the almost 1,700 citations in the first decade of the millennium extracted from the National Library of Medicine's PubMed online search engine using the keywords "adherence" and "compliance" in combination with "schizophrenia" (Fig. 2).

However, studies on treatment adherence are commonly vitiated by shortcomings that inherently interfere with the possibility of valid measurements [28, 37–42]. In particular, the available methods of assessment cover a very large number of approaches: for example, directly observed therapy, clinical response, patient's diaries and dedicated interviews, reports concerning factors, attitudes and opinions that can influence the adherence process, indications of individual autonomy in taking medicines, specific queries directed to significant others, judgement of the treating physician or, more broadly, the provider, chart reviews, formal pill count, rates of refilled prescriptions, microelectronic monitoring

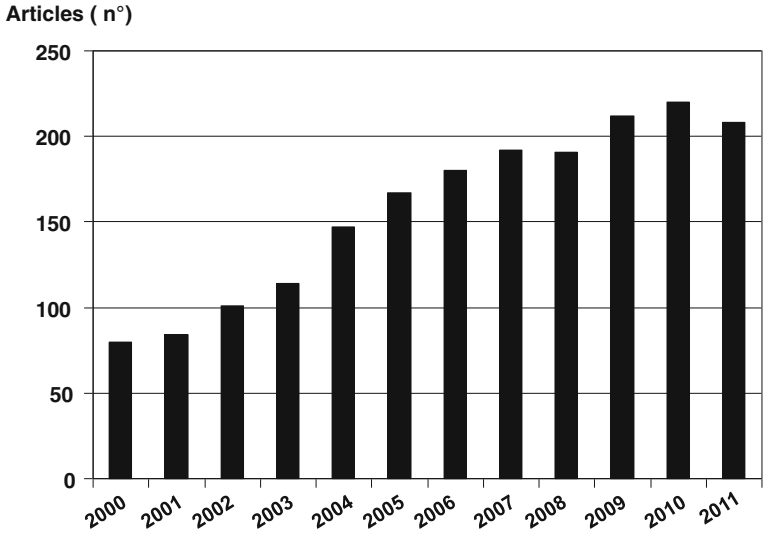

Fig. 2 Annual MEDLINE citations of the keywords "compliance" and "adherence" in combination with schizophrenia: period 2000–2011

measures such as MEMS, changes in physiologic markers, drug concentrations and analysis of tracer substances in body specimens.

Methods differ in many aspects. Some are direct, others indirect, and in both cases it is possible to distinguish between approaches that are objective or subjective, qualitative or quantitative and self-reported or informant reported [34, 37, 38, 42–49]. Furthermore, the many measuring methods allow for alternative instruments.

Despite the complex scenario, heterogeneity among distinct measures of medication adherence is generally not sufficiently discussed. This is wrong. The degree of concordance and correlation between independent methods of measurement is fairly scant. The literature on this issue appears unequivocal. For example, when three dedicated questionnaires, one clinician rated and two patient rated, were applied to 329 schizophrenia patients living in four European cities and participating in the QUATRO study [39], a concordant label of non-adherence was attributed to only 4 % of the cases; rates of individuals classified as non-adherent by any single questionnaire fluctuated widely: 54.9, 20.4 and 14.1 %, respectively. A measurement effect has also been documented in a group of patients with a first episode of psychosis tested with four methods [50]: the rate of adherence was estimated at 91 % by family members, 83 % by patients, 76 % by clinicians and 73 % by pill counting. Similarly, the application of a medical record-based MPR over 1 year and a five-point patient's self-report scale to 1,579 US subjects with a diagnosis of schizophrenia [51] showed that only 8.8 % of the sample classified as non-adherent according to one measure was also non-adherent for the other measure. Furthermore, in a small group of patients with schizophrenia followed for 3 months after discharge from hospital [52], 77, 65 and 40 % of the total sample

were considered poorly adherent according to plasma drug concentration, pill count, or self-assessment, respectively. Poor correlation between the same three measures was also detected in another independent 3-month study [53]: 9, 23 and 55 % of the sample were judged adherent when pill count, blood level data or patient's self-reports were considered. Even poorer correlations between different methods for measuring adherence emerge when electronic monitoring was considered. For example, the application of self-reports, physician reports, pill counts, electronic monitoring and drug plasma concentration [54] showed not only that pill counts and MEMS were strongly correlated with each other and weakly correlated with self-reports and physician ratings but also that drug plasma levels were not correlated at all with any other measure of adherence. Similarly, a 3-month study limited to 25 subjects with schizophrenia reported rates of 48 and 0 % non-adherent patients according to a MEMS daily adherence below 70 % or a clinician rating score equal to or less than four [55]. In a subsequent report by the same group [56] on 61 patients with schizophrenia or schizophreniform disorder followed for up to 6 months, electronic monitoring was challenged against three visual analogue scales elaborated by the prescriber, the research assistant and the patient. MEMS registered 57 % of non-adherent patients, which was close to the 54 % reported by the research assistants but higher than the 7 % estimated by the prescribers and the 5 % indicated by the patients. These studies suggest that MEMS plausibly detects greater non-adherence rates than other methods. An 8-week study [57] of 51 Korean outpatients with schizophrenia treated with a single antipsychotic medication reported similar results: the rate of non-adherence according to MEMS was considerably higher (41 %) than the 26, 8, and 8 % for patient's self-report, pill count and clinician rating scale, respectively. Notably, 38 % of the patients labelled adherent by the clinician were judged non-adherent by MEMS. Given the weak concordance between the different measures, it is far from surprising that results on the clinical consequences of poor medication adherence are appreciably influenced by the specific method of measuring used in the different studies [58].

However, there is some evidence of good correlation between different measures of medication adherence. For example, in an observational, prospective, large scale, German study [59], physician's and patient's ratings of compliance showed 93.2 % concordance. However, irrespective of the measure used, the presence of very high compliance rates, more than 80 %, makes the validity of the results questionable.

An obvious measure effect is evident when independent studies on adherence or compliance are reviewed. For example, in a comparative analysis of findings based on patient interviews, urine tests or clinician assessments, the estimates of compliance were 52, 60 and 72 %, respectively [40].

Thus, that different measures of adherence fail, *de facto*, to estimate the same trait seems very plausible. Even a superficial comparison between the main characteristics of individual instruments of measuring corroborates this suggestion.

For example, a formal impression of treatment adherence is in sharp contrast to the use of rigorously standardised methods of quantification. Measures that are over-inclusive and charged by relevant confounders (e.g. the drop-out rate) are conceptually far apart from other measures (e.g. the drug-attitude inventory) where the focus on a partial aspect of adherence may lose touch with a global approach to medication-taking behaviour.

Another issue of divergence between studies involves the adoption of a dimensional or categorical approach for measuring adherence. So far, the latter has been more popular, probably because it is easier and more immediate: a simple all-or-nothing partition of medication adherence according to a pre-ordered cut-off. However, the categorical approach has some weak points. For example, the cut-offs used in independent studies vary and the preference for one or another threshold seems largely arbitrary, in the absence of a solid base with a predefined clinical effect. It is also true that definite cut-offs to separate adherent patients from non-adherent patients could be clinically meaningful in the case of particular clinical characteristics (e.g. symptom severity) but not necessarily so when the focus is on another index (e.g. long-term prognosis). A supplementary criticism involves the issue of partial adherence. The "notion of noncompliance as complete, wilful cessation of all antipsychotic medications is not an accurate representation of actual medication-taking behaviour among outpatient populations with schizophrenia" [60] because many subjects should be classified as partially compliant rather than non-compliant. Furthermore, "partial compliance may take several forms, including taking an amount that is consistently less than recommended, irregular ('on-and-off') dosing behaviour, and having discrete gaps in antipsychotic therapy" [60]. This adds complexity to a vexing and already complex topic. The categorical approach counts all patients posited above a definite threshold as adherent but it does not consider that, for a non-negligible minority of individuals, deviation from the prescribed medication consists of taking medicines in excess. For example, in a large-scale study involving 3,968 veterans treated with antipsychotics in monotherapy, the rate of medication over supply was 7.6 % [61]. Therefore, in practice, the label adherent is applied to a mixed population of truly adherent and over-adherent individuals.

Thus, a dimensional approach seems inherently preferable, because the use of a continuous measure is more indicated when the phenomenon under scrutiny is multifactorial in origin and devoid of an unequivocally validated discriminatory threshold. Both these requirements are fully satisfied in the case of medication adherence. Nevertheless, the application of a purely dimensional design may be problematic in practice, because it commonly generates results that are hard to interpret and require wide sample populations. Partition into a number of predefined classes acting in continuity with each other could be a reasonable strategy to bypass these limitations.

Each method for measuring medication adherence has specific and appreciable pitfalls. For example, phenomena such as aversion to pharmacologic treatments and unjustified beliefs about convenience or the need to please doctors and significant others may frequently induce patients to voluntarily over report their adherence.

This manipulation primarily damages those measures directly or indirectly based on the personal reports of the patient but may also undermine more objective approaches, such as direct pill counts, MEMS, photos, monitoring of drug concentration and analysis of a tracer substance. However, direct pill counts, MEMS and photos certify that the blister is empty, the bottle has been opened or the pills are in the palm of the hand but do not prove that the patient has really ingested the therapy as prescribed. Physiologic markers and levels of drugs or tracer substances investigate medication intake during the few days immediately before the assay but may offer distorted information about adherence behaviour outwith this specific time frame. Unfortunately, many patients are susceptible to the white-coat compliance phenomenon [29] immediately before a medical visit and medication-taking behaviour then declines in the interval between two scheduled visits [62]. Some adherence measures may contribute to bad estimates in the absence of deliberate manipulation. For example, patient's difficulties in recalling detailed information about drug intake may inflate or deflate the rates of poor adherence when the source of information is based on direct reporting. The same misleading consequences may occur when inattentive relevant others are deputed to quantify the ability of the patient to follow regularly the established medication regimen.

Physicians may be not reliable in detecting poor medication adherence [63–66]. Psychiatrists, in particular, have been reported to be especially prone to underestimating the adherence of their clients [65, 67, 68]. The conclusion of a recent large-scale study [67] carried out in Germany and involving 5,729 patients with schizophrenia and 699 psychiatrists working in hospitals or in private practice is representative in this regard. When specifically interviewed, the treating physicians estimated 68 % of unintentional partial compliance during the last month and 69 % intentional lifetime partial compliance. Both these values exceed the mean and modal percentages generally observed when other adherence measures are used. If confirmed, the poor performance by psychiatrists to identify patients with correct medication-taking behaviour could be relatively atypical, because doctors in other specialties have generally been found to be more prone to overestimate compliance [69]. However, contrasting results also exist. For example, in a 1970 VA study [66] reporting "that therapists erred in 20 % of their prediction", the wrong prediction resulted in 71 % of the cases "in the direction of believing that the patient was not taking his drug or drugs as prescribed when in fact he was".

The frequencies of poor adherence obtained using direct assays of antipsychotics may be equivocal. For an identical dose, blood levels are subject to relevant interindividual variability. Furthermore, the presence of poor and ultra-fast metabolizers may contribute to false positives and false negatives in the non-adherent population; because two corresponding cytochrome P450 genotype variants produce opposite effects on drug degradation [70, 71], a regular taker may be spuriously labelled as poorly adherent or non-adherent. The current trend for multi-racial societies requires that attention must be paid to the effects of cytochrome genotyping on medication adherence. Various ethnicities differ in the global distribution of the individual alleles involved in classifying patients' according to metabolic

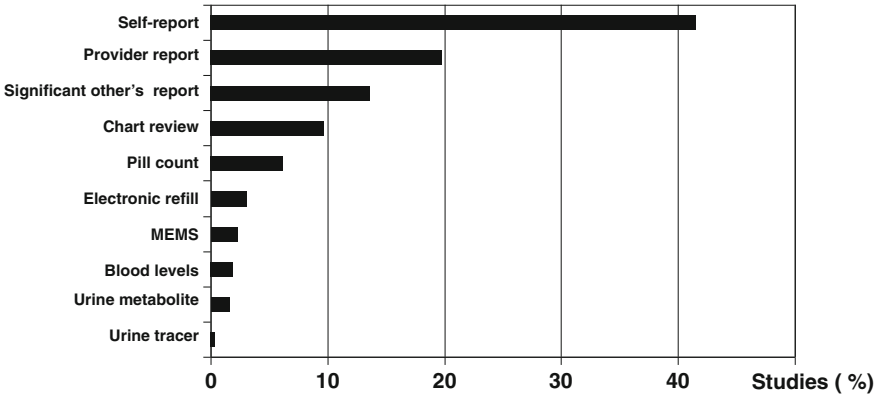

Fig. 3 Most utilised methods for measuring adherence to antipsychotic medications (adapted, with permission from Velligan et al. (2006), ref n deg 37)

status [72] and this implies a supplementary, ethnic-dependent risk of erratic estimates of medication adherence when direct assessments of drug plasma levels are performed.

Highly elaborate questionnaires and interviews, microelectronic monitoring, assays of the medicines in body fluids or, more broadly, the use of procedures that deviate from daily clinical routine may also exert distortive effects on habitual medication-taking behaviour, because they selectively channel the patient's attention on the phenomenon [37, 42].

Methods of measuring such as MEMS, drug monitoring and assays of tracer substances in body fluids have some important limitations. In particular, they are expensive and, therefore, their use contrasts not only with the need to obtain data from large, representative samples of patients but also with current worldwide financial constraints. Furthermore, these approaches may be perceived by some patients as intrusive or dangerous to the point that formal dedicated informed consent is required.

Given the long list of inherent weaknesses that affect almost all measures of medication adherence and the lack of a universal standard of reference, it is easy to see why the choice of one method over another varies greatly among studies. In a recent review of 258 studies [37], the fact that no measure of medication adherence was reported to have the lion's share (Fig. 3) is well representative of this reality.

Frequency of Poor Adherence to Antipsychotics

Awareness that a relevant proportion of people with schizophrenia do not take medicines as prescribed was already manifest when neuroleptics entered the market and mental health community care was in its infancy. A 1962 study [32] of patients with schizophrenia discharged from eight London mental hospitals may be

paradigmatic, because it reported that 44 % "of the courses of a drug prescribed were probably not taken as intended by the doctor", with rates of drug courses classified as "taken but definitely not as ordered", "taken but probably not as ordered", "definitely not taken at all", and "probably not taken at all" posited at 28, 8, 3, and 5 %, respectively. Almost contemporaneously, in a systematic study [31] of all patients with a diagnosis of schizophrenia or schizophreniform state discharged from the West House Division of the Royal Edinburgh Hospital between January 1959 and December 1960, it was emphasised that, "of the 124 patients who had been prescribed neuroleptics at some time during the follow-up period, 54 % probably took them as ordered, 46 % did not take them as ordered".

These first claims have been corroborated in the decades since then. In a 1986 review [63] of 21 articles published between 1958 and 1984 and involving almost 3,000 patients, non-compliance with oral first-generation antipsychotics, defined as "any significant deviation from the prescribed medication", was estimated to range between 10 and 76 %, with a median value of 41 %. About 10 years later, another review [64] of "fifteen subsequent studies using varying definitions of noncompliance and many mixing patients taking oral and depot medications reported a median 1-month to 2-year noncompliance rate of 55 %", with a range from 24 to 88 %. In a review [40] of 24 articles published over a 20-year period and involving 26 groups of patients and 3,590 individuals, the compliance rate was found to fluctuate between a minimum of 24 % and a maximum of 90 %, with an overall mean of 58 %. However, this impressive rate of variability seems largely due to the common inclusion of studies based on disparate measures and definitions of compliance.

For example, at the beginning of the millennium, a review [47] of 39 articles published between 1981 and 2002 compared three different definitions of medication adherence. According to the broadest definition, which was applicable to all the studies, the non-adherence rate ranged between 4 and 72 %, with an unweighted mean and median value of 40.5 and 40 %, respectively. These figures remained substantially unchanged when the analysis was restricted to the 10 articles that adopted a more conservative definition of adherence, "regularly taking medications as prescribed", and only trained personnel were used to assess medication-taking behaviour. When the selection of the articles involved an even stricter working criterion, "taking medications as prescribed at least 75 % of the time", the unweighted mean non-adherence value increased to 47.3 %, with a median rate of 47 %. One year later, another systematic review [73] judged 86 studies suitable for re-analysis. Of the 23,796 patients, 5,790 had a diagnosis of schizophrenia, 6,372 had psychosis in general and 11,634 had severe mental illness. The overall weighted mean rate of patients who were found to be non-adherent to medication and/or selected appointments was 25.8 %; the proportion of individuals who did not take pharmacologic therapies as prescribed was 29.7 %, which was slightly but not significantly higher than the proportion of the group that missed the appointment (24.3 %).

In addition to the different measurement methods, other factors are also likely to play a major causative role in discrepancies between results. The setting and the context in which the treatment is carried out certainly belong to this list. Regularity in taking medicines may be influenced by the prescribed drug, referral as inpatient rather than outpatient, compulsory therapies, enrolment from clinical trials or the real world and access to services that are engaged in treatment adherence in different ways. Given the current widespread success of a model of psychiatric care founded on community interventions, the results of the earliest literature on medication adherence by people with schizophrenia seem hardly transferable to the practice of today. Problems of comparability also derive from the fact that, in the clinical practice of the last 15–20 years, second-generation antipsychotics have substantially replaced first-generation agents, which were at the centre of the initial reports on adherence by people with schizophrenia.

The duration of follow-up can also affect medication adherence because of the reported inverse relationship between the two phenomena [28, 55, 74, 75], a relationship that probably starts early after the start of the therapy. Compliance is also likely to vanish over time in patients treated with depot antipsychotics [76]. However, the link between the level of adherence and the length of exposition to medicines has been refuted in other reports. For example, a revision of the literature [73] has failed to show different rates of medication adherence between cross-sectional and prospective studies based on follow-up lasting less than 6 months, between 6 and 12 months or more than 12 months. A preference for the hypothesis of a decrease of adherence with time is also supported by some clinical considerations. In particular, it seems not only that the longer the duration of the illness, the higher the susceptibility for an exacerbation of symptoms leading to poor medication adherence but also that the longer the asymptomatic or quasi-asymptomatic period, the lower the patient's perception of the need to continue therapy, with the consequence of an increased risk for relapse [34, 77, 78]. Despite the evidence, studies continue to refer to periods of variable length or do not explicitly report the duration of follow-up. Therefore, comparisons between studies are not possible.

A supplementary source of heterogeneity in the prevalence of medication adherence comes from the frequent recruitment of small or relatively small samples. The epidemiology of medication-taking behaviour is the ultimate result of a complex, multi-determined process and is at high risk for selection bias when the study population is not numerically representative.

Several pitfalls affect the construct of the various epidemiologic studies on adherence to antipsychotics to varying degrees, and therefore definite conclusions about the true prevalence of the phenomenon cannot be drawn. However, even when only reports that have used similar measures of medication adherence and challenged samples of more than 1,000 patients followed in a naturalistic setting are considered, an appreciable variability in adherence rates remains between independent studies. Few citations seem sufficiently paradigmatic in this regard. For example, in a population-based study [79] of 6,662 Quebec residents who had a diagnosis of schizophrenia and were treated as outpatients with second-

generation antipsychotics, 67.5 % of the sample persisted with the same class of medication because they "filled at least one prescription … in the 45 days before the first anniversary of treatment initiation" and 78.6 % of the persistent group were deemed compliant, as indicated by 80 % or more continuous medication availability. Another study [80] involving 63,214 patients included in the VA National Psychosis Register and treated with oral antipsychotics due to schizophrenia or schizoaffective disorder reported that "approximately 40 % of those receiving one antipsychotic during the year and 38 % of those receiving two different antipsychotics had MPRs less than 0.8, indicating poor antipsychotic adherence". A subanalysis of patients receiving only one antipsychotic medication has also documented similar percentages of poor adherence, 41.5 and 37.8 %, among the 23,072 patients prescribed a second-generation antipsychotic and the 25,931 patients treated with a conventional agent. Furthermore, "eleven percent of [the patients] receiving one antipsychotic and 19 % of those receiving two antipsychotics during the year received more days' supply of medication than would be required to take their antipsychotics as prescribed". A study [81] of Medicaid beneficiaries with schizophrenia treated in San Diego with oral first-generation or second-generation antipsychotics concluded that 24 % of the patients were non-adherent, 16 % were partially adherent, 41 % were adherent and 19 % were excess fillers. This result is in contrast to the report of an MPR-based 1-year study [60] on a cohort of 4,325 California Medicaid patients who were prescribed antipsychotics for the treatment of schizophrenia; less than 16 % of the sample presented an MPR below the 70 % threshold. Similarly, in a multi-site, prospective, naturalistic study [51] involving 1,579 schizophrenia patients extracted from the US-SCAP database and treated in usual care settings with any oral antipsychotic, the 1-year rate of individuals with an MPR of 80 % or less was only 10.2 %.

Persistence of appreciable differences in the results among studies characterised by relevant similarities in design may be seen as a proof of how patient settings and general context may act as confounders. A comparison [82] between patients with schizophrenia who were resident in two Canadian provinces, Quebec and Saskatchewan, documents this. Although the two populations were treated similarly in routine community practice, and for both groups the prescription was limited to risperidone, olanzapine or quetiapine, the index data were taken on the day of the first prescription of one of the three atypicals, and the MPR was used to measure medication-taking behaviour, patients from the two provinces diverged in the rate of individuals falling below the cut-off of an MPR of 80 %. Among the 40,854 and 3,291 patients resident in Quebec and Saskatchewan, a status of moderate to poor compliance was detected in 39 and 55 % of the two sample populations, respectively. The disproportionate size of the two samples could have reasonably contributed to the discrepancy in the results, even though the smaller cohort was probably more representative than the larger one because publicly funded health insurance in Saskatchewan covered a larger proportion of residents.

All the examples reported so far lead to an univocal conclusion: the amount of epidemiologic data on adherence to antipsychotics could increase further but expansion of the references is likely to have little impact on the possibility of stronger consensus on the rate of poor medication-taking behaviour.

The descriptive epidemiologic approach to adherence has promoted deeper understanding of some other relevant aspects of the phenomenon. The first aspect concerns the time frame between hospital discharge or the start of therapy and the emergence of poor adherence. Knowledge of this interval is not trivial in the planning of dedicated, incisive community care interventions. A large, observational, cohort study [83] of patients with schizophrenia from the Maine and New Hampshire Medicaid programmes demonstrated that almost half of the prescription gaps from 1 to 10 days occurred in the first 50 days after initiation of a second-generation antipsychotic, with an appreciable proportion of the gaps occurring in the first month. Furthermore, the rate of subjects who failed to take antipsychotics as prescribed within the first 7 to 10 days after transition from inpatient to outpatient status has been reported to range between 15 and 25 %, in relation to the measure of adherence used [84]. Early emergence of non-adherence to antipsychotic medication has also been observed in recent-onset patients, as indicated by the finding that a "moderate or greater nonadherence typically began approximately six months after clinical stabilization" [85]. The report, based on de-identified computerised pharmacy records from 1,157 US pharmacies, that patients "who had not filled a prescription for an antipsychotic during the 180-day period prior to the index date had a … ten-fold increase in the risk for medication discontinuation at the start of the therapy" [86] gives further indirect support to the idea that the time period around the start of the therapy is crucial for patients with schizophrenia to persist and adhere to their therapy. This very short interval is not surprising. In clinical routine, rehospitalisation soon after discharge is common among people with schizophrenia spectrum disorders. Furthermore, early occurrence of poor adherence is not confined to antipsychotics and schizophrenia but seems to represent a generalised event that is far from new. For example, almost half a century ago, it was reported that 3 % of 2019 prescription orders in general medicine were not filled within 10 days [87].

Another issue refers to the persistence over time of a defined adherence status. As emphasised earlier, non-adherence seems to become more diffuse as the disorder progresses. For example, follow-up of a group of 127 actively adherent patients with schizophrenia showed that 75 % remained adherent at 5.2 months and 50 % at 13.7 months, and, more broadly, that "the risk of becoming nonadherent was fairly even across the 22 month study period" [88]. This finding agrees with the observation [74] that, in patients with schizophrenia, the prevalence of discontinuation or interrupted use of antipsychotics was approximately 50 % after 1 year and 75 % after 2 years. Nevertheless, once established, non-adherence seems to have a discrete persistence, at least in the absence of dedicated interventions. The switch from a poor to a good medication adherence status has been reported to occur fairly quickly with the possibility of transition decreasing substantially with time [88]. Reports that MPR values significantly correlated with

each other over a 3-year period [89] and that previous adherence was the best predictor of future adherence [51] supports the proposal that individual proneness to poor medication-taking behaviour is expressive of a relatively stable trait. In agreement with this, it was found that during the 4 years after an index discharge from hospital, "the majority of patients identified as medication noncompliant … continued being noncompliant… after subsequent readmissions" [90]. The stability of poor adherence cannot be dismissed as irrelevant, because it supports the uncommon use of repeated measures and just the *pre-post* comparison in trials on the efficacy of interventions aimed at improving medication adherence.

Another clinically relevant chronologic issue pertains to the stage of the disorder at which poor adherence to antipsychotics becomes manifest. Overall, the literature indicates high rates of poor adherence among patients with schizophreniform disorder, first-episode schizophrenia or, more broadly, early schizophrenia [19, 91–97]. An experience derived from the Suffolk County Mental Health Project [95] is definitely representative of this. During the year after discharge from a first admission, 63 % of the patients had one or more gaps, defined as "any discontinuation in the use of antipsychotic medication, whether initiated by the patient or by the physician"; gaps initiated by the patient, the physician or jointly occurred at rates of 73, 16 and 11 %, respectively. Similarly, in a group of 605 patients with first-episode psychosis, 33.7 % of the patients were classified as fully adherent, 47.4 % failed to take medications for at least one phase of 1 week, and 18.8 % persistently refused medication [97]. Some evidence also exists that non-adherence to medication regimens in the early course of schizophrenia could be even more frequent than in the chronic phases of the disorder. For example, in a systematic review of 83 studies [73], the weighted rate of non-adherence to medication regimens and scheduled appointments was 46.9 % in first-contact patients, 23.2 % in those already undergoing treatment, and 53.3 % in those with a history of low adherence. The presence among patients in the early stages of their psychosis of a very high and possible heightened susceptibility to poor antipsychotic medication-taking behaviour fits well with the Health Belief Model [64, 98], in which medication adherence is considered to be a dynamic process of "the patient's beliefs about need for treatment and the benefits of treatment weighed against the negative aspects of treatment" [94]. Patients with schizophreniform disorder, first-episode schizophrenia or recent-onset schizophrenia are indeed "just beginning to come to terms with having a psychiatric disorder and have not been in treatment long enough to recognize the necessity of adhering to their medication regimen" [85].

Epidemiologic studies are inconclusive regarding the popular perception that people with schizophrenia are at special risk for poor medication adherence because of their psychopathology. The experimental evidence does not seem to substantiate this belief. For example, a subanalysis of the Canadian Community Health Survey database [99] centred on a sample of 6,201 individuals taking psychotropic drugs has indirectly indicated that different psychiatric conditions share a similar medication-taking behaviour; non-adherence to antipsychotics, sedative hypnotics, anxiolytics, mood stabilizers and antidepressants was found in

34.6, 34.7, 38.1, 44.9 and 45.9 %, respectively. However, the size of the group of patients taking antipsychotics, only 168 individuals, seems too small to ensure accurate estimates. In addition, the current literature on medication-taking behaviour suggests that there are large overlaps in the frequency of poor medication adherence among patients with schizophrenia and individuals with other medical or psychiatric conditions [40, 64]. However, a great deal of evidence on this issue comes from a patchwork of studies that, having been carried out independently, are at high risk for an unbalanced distribution of many sources of variation, particularly adherence measures. Furthermore, studies on people with schizophrenia carried out before the turn of the millennium have commonly used weaker measures of adherence than those used in research focused on subjects affected by a medical condition [40].

Similarity of compliance rates across therapeutic areas has been reported only when studies using electronic monitoring devices were reviewed [100]. Therefore, before concluding that the rates of poor adherence to prescribed medicines are similar across diseases and disorders, more direct evidence needs to be acquired. Head-to-head comparison between distinct clinical conditions is one of the most feasible strategies, even though this design is also charged with interpretative difficulties, such as the risk of spurious conclusions due to different diffusion of community care interventions among the various branches of medicine. In this regard, among a group of revolving door patients who met the RDC for schizophrenia, schizoaffective disorder, major depressive disorder or bipolar disorder, medication non-compliance was not found to be "associated more commonly with any of the four specific diagnostic categories" [101]. Intra-subject comparisons of adherence to different classes of medicines in people with comorbid disorders is a reasonable alternative approach that promises to offer superior methodological guarantees, but this experimental strategy has so far produced inconclusive evidence. Nevertheless, it seems of interest to cite a large-scale study of VA patients with schizophrenia who had diabetes and hypertension in comorbidity [102]; this study not only reported adjusted ORs of poor adherence "significantly higher for hypoglycemic and antihypertensive medications than for antipsychotic medication" but also significant associations "between the MPRs for each physical condition and patients' antipsychotic medication". This last finding suggests a generalised pattern of medication-taking behaviour that crosses different disease and drug classes. It seems plausible that medication adherence is also charged with supplementary illness-specific and/or drug-specific contributors because "information about antipsychotic adherence explained only 13 and 16 % of the variance in patients' antihypertensive and hypoglycemic MPRs"[102]. In addition, a study of non-demented middle-aged and older VA outpatients with schizophrenia [103] confirmed that poor adherence was "equally problematic for both antipsychotic and nonpsychiatric medications" but failed to replicate the presence of the correlation between the 12-month cumulative mean gap ratio for antipsychotics and those for antihypertensives, antihyperlipidemics and antidiabetics.

Consequences of Poor Adherence to Antipsychotics

The interest in poor medication adherence resides not in the phenomenon itself but in its consequences. Different mechanisms may be involved in the transformation of non-adherence into sequelae of clinical relevance. Some mechanisms refer to reduced adherence, others to increased adherence.

In particular, in the presence of a status of subadherence, two main biological pathways may be advanced. One is more applicable to patients with occasional failure to take medicines as prescribed and assumes that, when the magnitude of the missed therapy is enough to settle receptor occupancy by antipsychotics at a level below the therapeutic threshold, this opens the doors to the re-emergence or recrudescence of psychosis [104, 105]. The other pathway is more relevant for patients with long-lasting poor adherence problems and involves the well-known assumption [106] that compensatory receptor supersensitivity induced by chronic administration of antipsychotics makes receptors prone to over react when an abrupt discontinuation of the therapy occurs. Under these circumstances, the withdrawal is likely to have psychotogen potential in itself, as indicated by the trigger of a rapid-onset supersensitivity psychosis. The old claim [107] about the need to escalate antipsychotic doses concomitant with an acute relapse seems compatible with a supersensitivity model of psychosis. Subtherapeutic receptor occupancy and supersensitivity psychosis have slim boundaries and are susceptible to reciprocal transition.

The presence of an over adherence condition has three main possible pathways. The first suggests that the practice, for any reason, of taking medicines more than prescribed may lack clinical interest because of a neutral impact on the course of schizophrenia. The second postulates that patients not completely satisfied with their therapies may decide to ingest a relative excess of antipsychotics in an attempt to self-medicate, which, when unsuccessful, may lead to treatment cessation, and thus to non-persistence. The third proposes that, when patients are over adherent, they inevitably become more vulnerable to the iatrogenic health effects of antipsychotics, and thus switch to under adherence, with a consequent increased risk for both a recrudescence of schizophrenia and a supersensitivity psychosis.

However, the recent report [108] of an association between medication adherence and superior increase in frontal lobe intracortical myelin volume after risperidone therapy also supports the hypothesis that clinical correlates of poor medication-taking behaviour depend at least in part on a failure to promote white matter development in individuals affected by a deficit of the normal myelinisation trajectory.

Whatever the underlying mechanisms involved, failure to follow antipsychotic therapy as prescribed activates a cascade of negative effects in people with schizophrenia (Fig. 4). This dramatic conclusion could be even worse considering that untreated schizophrenia has been reported to exert a neurotoxic effect *per se* [109].

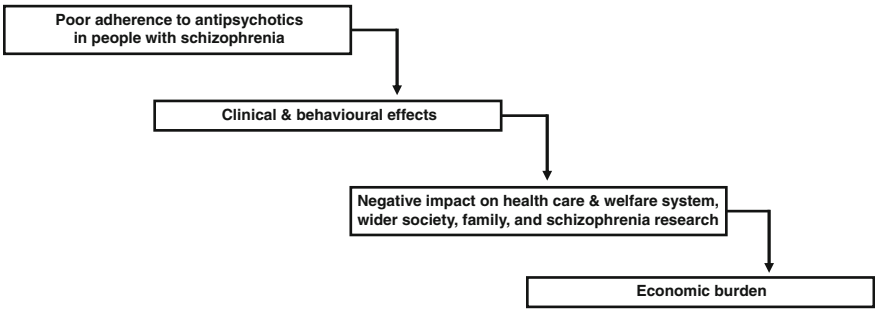

Fig. 4 Cascade of consequences due to poor adherence to antipsychotics in people with schizophrenia

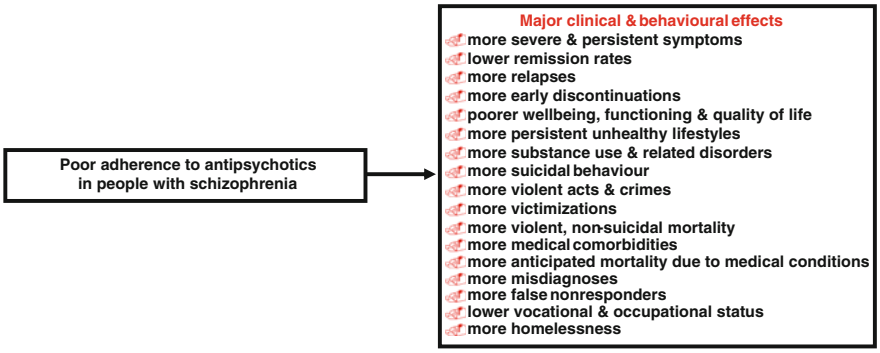

Fig. 5 Clinical and behavioural consequences of poor adherence to antipsychotics in people with schizophrenia

The strength and consistency of the effects played by poor medication adherence vary in relation to the specific consequence that is under consideration. Furthermore, most studies have a cross-sectional design that makes it impossible to specify which comes first when a chicken-and-egg situation related to a bidirectional interrelationship exists. Unfortunately, a number of associations between poor antipsychotic medication-taking behaviour and schizophrenia are at least potentially bidirectional, because poor adherence may worsen the disorder and definite features of the disorder may promote poor adherence. Furthermore, the two factors in the relationship may influence each other reciprocally. To conclude that poor medication adherence acts as a risk factor for a definite schizophrenia-related variable, longitudinal studies are certainly preferable because they could potentially settle the chronologic sequence of the two components of the association. However, longitudinal studies also frequently have the inherent limitation that interrelatedness between adherence and clinical variables does not necessarily imply an exclusive causal relationship.

Clinical Consequences

A great deal of evidence accumulated over the years emphasizes that the failure to follow antipsychotic therapy as prescribed interferes with symptom severity, short-term and long-term outcome and prognosis, degree of autonomy and functioning in daily life, the presence of comorbidities and the risk for violence, illegal acts, suicidal behaviour and, possibly, death in general (Fig. 5).

Symptom Severity Despite some negative findings, comparisons with individuals who follow doctor's prescriptions strongly support the conclusion that patients with schizophrenia who are poorly adherent continue to be afflicted by a more severe symptomatology [51, 57, 89, 93, 110–118]. Some specific domains of psychopathology, the positive cluster in particular and even some individual symptoms, such as conceptual disorganisation, lack of insight, poor attention and stereotyped thinking, are likely to be responsible for this unfavourable situation.

The impact of medication adherence on the clinical picture is likely to have appreciable relevance, because a regression analysis based on data from a 1-year naturalistic study [116] predicted an increase in PANSS total score of 3.1 points for each 20 % drop in treatment compliance.

Clinical Response The influence of poor medication adherence on clinical response of patients with schizophrenia treated with antipsychotics have undergone experimental evaluation. A post hoc analysis of an 8-week trial [117] has shown how any additional day of non-adherence "reduced the likelihood of achieving response at study end by 6 %".

Moving from clinical response to remission, a German prospective, randomised, observational, 2-year follow-up trial of 2,960 patients with schizophrenia [119] seems particularly representative. The study reported that, compared with patients who complied with antipsychotics, those who did not comply, 36.5 % of the total sample, had an OR of 0.73 for achieving symptomatic remission, defined as "receiving a CGI-Schizophrenia severity score of absent to mild in assessments of overall severity, and positive, negative, and cognitive subscores" [119]. In contrast, no relationship has been reported between non-compliance and functional remission, defined as a positive occupational/vocational status. The discrepancy between symptomatic and functional remission may be explained by the fact that the latter implies possibilities of access to opportunities largely independent of how much a patient follows the prescriptions of the treating physician. Medication adherence has also been reported to exert a negative influence on the chances for and time to remission of first-episode populations [120].

Another study [121] failed to demonstrate, over a 5-year period, an association between the percentage of time spent in taking antipsychotics and symptom remission. However, this last negative finding was extracted from a sample population in which "long-term medication adherence was very high, since subjects usually resumed medication following staff interventions or the return of

symptoms" [121]. Therefore, the possibilities for generalisation of the results seem questionable.

Relapses The association between poor medication adherence and psychotic relapses seems especially solid [58, 64, 85, 121–132]. In particular, in a group of first-episode patients with schizophrenia, schizophreniform disorder or schizoaffective disorder recruited in Hong Kong and followed for 3 years, subjects "taking less than 70 % of prescribed medication" had a 57 % cumulative relapse rate, a much higher value than the 36 % found in patients with good adherence [124]. When, in the same study, only patients with schizophrenia were considered, the influence of poor medication adherence on relapse risk remained substantially unchanged: at the end of the first, second and third year of follow-up, the cumulative relapse rates were 20, 31 and 37 for subjects with good medication adherence and 36, 64 and 64 % for those with poor adherence. In a logistic regression model applied to the same dataset, non-adherence was found to be an appreciable predictor of relapse, with an OR greater than seven. Another 5-year follow-up study of patients with a first-episode of schizophrenia or schizoaffective disorder who responded to initial therapy with antipsychotics [123] reported similar results; treatment discontinuation against the advice of the clinician implied an HR of 4.57 for a second relapse in the group of subjects who, after an initial relapse, were prescribed to continue antipsychotic medication for the remainder of the trial.

Although preferentially supported by studies of patients with first-episode schizophrenia, the negative influence of poor adherence to antipsychotic medication on relapse risk is a phenomenon that is commonly present at all stages of the disorder. For example, in a review [64] of seven independent studies, it has been reported that schizophrenia "patients rated as noncompliant have a 6-month to 2-year risk of relapse that is an average of 3.7 times greater than patients rated as compliant". In addition, a logistic analysis based on data drawn from the US-SCAP study [126] has reported an OR of 1.79 for relapses in patients presenting a non-adherence status. Furthermore, it has been estimated that "at the 1 year point, approximately 68 % [of relapses] is owing to loss of neuroleptic efficacy and approximately 32 % is owing to neuroleptic noncompliance" [122].

A brief period of medication non-adherence is probably enough to induce a relapse. A study [85] of patients with recent-onset schizophrenia or schizoaffective disorder treated with risperidone reported an HR of 5.8 for relapses after mild non-adherence, defined as compliance of 50–75 % of the prescribed medication for at least two consecutive weeks during the follow-up period. Similarly, among patients with first-episode schizophrenia followed for 1-year after discharge from hospital, more subjects classified as non-compliant, because they "had used less medication than prescribed or completely skipped … medication for ten consecutive days" were represented in the relapsed group than in the non-relapsed group (70 and 25 %, respectively) [125]. Underlying the statement that "there is very little leeway for brief gaps in oral antipsychotic medication used or dosage reductions" [85], the last two studies highlight the need for assiduous and vigorous

interventions aimed at improving adherence, even when only brief deviations from the prescribed antipsychotic regimen are suspected.

Given the unfavourable impact on the risk of relapses and their duration, poor adherence to antipsychotics could also lead to long-term secondary effects associated with recurrences such as the loss of responsiveness to these agents and the consequent needs to increase the doses concomitant with increased frequency and duration of psychotic breakdowns [133–135].

Early Discontinuation Some evidence exists that medication adherence influences the probability of early discontinuation from therapeutic programmes. For example, in an 18-month study of 99 patients with schizophrenia followed by the University Psychiatric Services of Brescia Spedali Civili, it has been observed that, compared with adherent patients, those classified as moderately or poorly adherent had relative risks of premature discontinuation for any reason that were 2.5 and 5.6 times higher, respectively [136]. Furthermore, according to a secondary analysis of a 52-week, randomised, double-blind, flexible-dose trial centred on the effectiveness of olanzapine, quetiapine and risperidone in patients with a first-episode of schizophrenia, schizoaffective disorder or schizophreniform disorder, "each point improvement on the medication adherence rating scale resulted in almost a 30 % reduction in the hazard of treatment discontinuation" [137]. The impact of medication-taking behaviour on rates of discontinuation does not seem restricted to long-term therapies, because the association has also been fully documented in an 8-week trial [117]. However, compliance scores for patients with first-episode schizophrenia enrolled in the EUFEST did not differ in relation to the discontinued–nondiscontinued dichotomy [138].

Wellbeing and Functioning Some findings suggest that the negative effects of poor adherence to antipsychotics may extend to wellbeing and functioning, social relations and activities of daily living in particular [59, 89, 119, 121, 139–141]. For example, non-compliance has been associated [119] with an OR of 0.73 for subjective wellbeing. Compared with non-adherent subjects, adherent patients have also been reported to present "significant and sustained improvements over the following 2 years in mental functioning, satisfaction with social life, satisfaction with basic needs, and general life satisfaction" [89]. Furthermore, patients who have improved compliance have been shown to improve their total score by 45.7 % for the SWN-k, a percentage definitely better than the 27.9 and 17.9 % found in subjects whose compliance was unchanged or worsened [59]. Overall, it seems reasonable to hypothesize that poor medication-taking behaviour contributes considerably to the WHO's listing of schizophrenia as the seventh leading cause of DALYs worldwide [142].

However, it cannot be dismissed that "evidence for interrelatedness between the course of compliance and subjective wellbeing" does not explain which variable has a causal effect and does not exclude a reciprocal influence [59].

Substance Use Disorders Non-adherence to antipsychotic medication has been associated with substance use and greater severity of alcohol-related problems [51, 89, 90, 101]. The observation [143] that, when compared with non-adherent non-depot initiators, non-adherent depot initiators are at higher risk for substance abuse before starting with depots gives further indirect weight to the association.

Despite the convergent support of a sufficient amount of evidence, the possibility of quantifying with precision the impact of medication-taking behaviour on the risk for substance use and related disorders remains arduous, because the two terms of the association influence each other reciprocally.

Suicidal Behaviour, Violence and Crimes Demonstrations of links between poor adherence to antipsychotics and suicidal behaviour, violence and crime in people with schizophrenia are robust.

With regard to suicidal behaviour, a meta-analysis of 29 case–control or cohort studies concluded that poor adherence to antipsychotics more than triples the suicide risk [144], thus confirming a 1984 report [145]. In addition, a large Canadian retrospective study reported a reduced risk of attempted and successful suicides among patients from Quebec with good compliance [82]. However, the finding has not been replicated among the residents of another province, Saskatchewan. The discrepancy in the results between the two provinces is plausibly due to the relatively low base rate of suicidal behaviour, which requires large samples to detect reliable associations. This prerequisite was satisfied much better in the Quebec sample (41,754 patients) than in the Saskatchewan group (3,291 patients). The link between suicidal attempts and poor adherence to antipsychotics has also been considered in other studies. For example, in an analysis of drug-dispensing records carried out in the Netherlands and involving a sample of 603 exclusive users of olanzapine or risperidone who were "suspected to suffer from schizophrenia", the adjusted relative risk for suicide attempts leading to hospitalisation "among patients with drug holidays was increased four-fold compared to patients without drug holidays" [146]. A higher risk among non-adherent patients also emerged in the SOHO study, which followed 6,731 outpatients with schizophrenia for 3 years [127]. Furthermore, in a sample of 36,195 California Medicaid subjects followed prospectively for 1 year due to ICD-9 schizophrenia [147], adherent patients presented lower rates of current and past suicide attempts compared with both non-adherent and partially adherent patients.

Although violence is only marginally associated with schizophrenia [148–150], poor adherence to antipsychotics was reasonably associated with increased proneness to this behaviour [51, 89, 151–158]. In particular, in a numerically representative sample of patients enrolled in the US-SCAP study and followed for a 3-year period [89], individuals with poor adherence to antipsychotics were reported to be more frequently violent, arrested or victims of crimes.

Furthermore, a non-adherent status over the first year has been found to lead to a 2.2 and 1.8 times increased risk for being arrested or victim of a crime in the successive 2 years, respectively. Data related to homicides seem to follow the

same trend. According to a Swedish national case–control study of patients with schizophrenia or other psychoses [157], it was observed that, compared with compliant patients, non-compliant subjects had an almost quadruple risk for homicide within the first 6 months after hospital discharge. Reports referring to the impact of improved medication-taking behaviour on violence risk constitute a valid countercheck of the strength of this association. In a trial involving patients with schizophrenia or related disorders who received services in the North Carolina public sector mental health system and were followed for a 3-year period [152], "compliance with prescribed medication 'most of the time' or 'all of the time' was significantly associated with reduced violence" and olanzapine was found to be superior to risperidone for the control of violence, largely as a consequence of a more pronounced positive effect on adherence. Another study by the same group [153] reached similar conclusions; an inverse correlation between medication-taking behaviour and violence was observed, and novel antipsychotics were shown to control violence better than conventional neuroleptics. This superiority was attributable to the presence of a cumulative effect between medication and compliance that was present with novel agents but not conventional agents. The trial also highlighted that long-lasting compliance with second-generation antipsychotics made the risk for violent behaviour almost negligible. The clinical potential of this finding, if confirmed, is obvious. Reports [151, 159] that involuntary outpatient commitment and administration of depot antipsychotics can reduce violent behaviour in people with severe mental illness are a further indication of the central role played by medication-taking behaviour on the risk for violence.

In general, the association of poor medication adherence with violence, assaultive behaviour and other crimes appear trans-diagnostic in nature, because it has also been found in patients affected by severe mental disorders other than schizophrenia [35, 149, 154, 155, 158–161].

In addition, evidence derived from the ECA study [148] suggests that the impact of medication adherence on violence is especially pervasive in the presence of a comorbid substance abuse disorder, as indicated by the observation that a mood disorder, schizophrenia or substance abuse were each associated with 3. 5, 8.4 and 21.3 % of subjects having violent behaviour, whereas the co-diagnosis of a mood disorder or schizophrenia with substance abuse increased the percentage to 29.19 and 30.30 %, respectively.

Distinct, so far unidentified, characteristics associated with problematic medication-taking behaviour may increase the risk of imprisonment. In a selected population of poorly adherent subjects, patients judged worthy of initiating a long-acting first-generation antipsychotic were reported to have an almost 4-fold higher probability of being arrested or jailed in the preceding 6 months compared with non-depot initiators [143].

Mortality Evidence of an association between non-adherence to antipsychotic medication and death for any reason also exists. In particular, in a retrospective large-scale study of more than 40,000 patients with schizophrenia, good

compliance status was found to be associated with HRs for death equal to 0.65 and 0.58 in the short term and long term, respectively [82]. This result seems to be reconcilable with the healthy adherence effect hypothesis [1] and contributes to explain the common observation that people with schizophrenia have a reduced life expectancy not only due to unnatural causes but also due to natural causes [162–173].

False Non-Responders When unrecognised, poor medication adherence aggravates the course of schizophrenia and promotes misdiagnoses and erroneous classification as non-responders among patients who do not respond because they fail to take medicines as prescribed. "The physician bases critical decisions in management and diagnosis on the patient's response to a therapeutic regimen. If he observes no response to a usually effective regimen, he may decide to change the treatment or he may even question his diagnosis" [69]. Common consequences of these misleading processes are increased doses of the medication to near or over the maximum permitted, the introduction or implementation of polypharmacy therapies and anticipation of switching from one antipsychotic to another. Data on 7,864 patients with schizophrenia or bipolar disorder who entered a Southeastern Medicaid programme [174] demonstrate this association. Compared with compliant subjects, partially compliant patients were shown to be 64 % more likely to switch from one antipsychotic to another or to increase therapy. Switching and augmentation strategies can lead to appreciable hazards; therefore their unjustified use should be avoided and judged reprehensible.

Societal and Health Care System Consequences

The different negative clinical consequences sustained by poor medication adherence reverberate inevitably on the health care system, the patients and their families and wider society (Fig. 6).

Health Care Services With regard to the consequences for health care services, a large preponderance of the literature supports the concept that poor adherence to antipsychotic drug regimens is an appreciable risk factor for frequent hospitalisation [51, 58, 60, 81–83, 89, 93, 111, 115, 127, 130, 131, 175–186]. A realistic snapshot of the dimension of the association may be offered by three small studies. In a group of revolving door patients with schizophrenia admitted to short-stay urban psychiatric units in New York, non-compliance was regarded as the most common suspected cause of relapse leading to new hospital admissions and was classified as the primary cause in 50 % of cases [178]. In addition, a study involving a diagnostically mixed group of patients reported a sharp contrast between the 6 % rate of non-compliant patients who incurred one hospitalisation and the 29, 30 and 34 % found among patients with 2–4, 5–10 or more than 10 hospitalisations, respectively [101]. In parallel, a case–control study [176] of

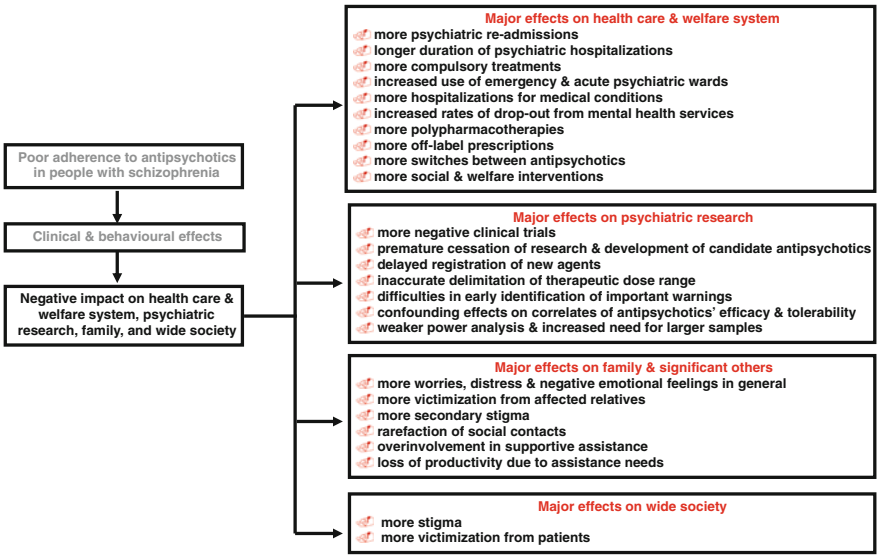

Fig. 6 Impact of poor adherence to antipsychotics on health care and welfare system, research, family and wide society

seriously ill patients with schizophrenia followed by community mental health centres in Mississippi reported that medication non-compliance was associated with the highest adjusted OR for rehospitalisation, [8. 18].

However, full validation of the strong relationship that exists between adherence to antipsychotics and the risk for psychiatric hospitalisation comes from some large-scale studies based on continuum or quasi-continuum measurements of adherence. In particular, in a large sample of VA patients with schizophrenia or schizoaffective disorder who "had an outpatient prescription for an oral antipsychotic medication between October 1, 1998 and September 30, 1999", the link between the two variables was well expressed by a U-shaped curve: a progressive decline in the rate of psychiatric admissions occurred as the patients' MPR approached one and a successive increase in rehospitalisations emerged when patients presented excess medication fills [179]. In particular, subjects with poor adherence or excess medication fill were 2.4 and 3.0 "times as likely be admitted during the study year than patients with good adherence". A quasi carbon copy analysis based on Medicaid beneficiaries with schizophrenia followed in San Diego County [81] confirmed that individuals classified as non-adherent, partially adherent, adherent or excessive fillers differed in the frequency of psychiatric hospitalisations: 34.9, 24.1, 13.5 and 24.8 %, respectively. Hospitalisations due to medical conditions were also affected by antipsychotic adherence, because "individuals who were nonadherent or excess fillers were about 70 % more likely to be hospitalised for medical care, and those who were partially adherent were about 30 % more likely to be hospitalised than those who were adherent" [81]. A

2-year prolongation of the period used for the inclusion of the patients [187] confirmed the association of adherence with the rates of both psychiatric and non-psychiatric hospital admissions. A Canadian study based on bipartition of patients into compliant and non-compliant individuals further consolidated the presence of an association between non-compliance and increased hospitalisation rates due to psychosis or medical conditions [82]. Specifically, patients with good adherence in the first year after the index prescription of an atypical antipsychotic had an all-cause hospitalisation adjusted HR of 0.65 in Quebec and 0.80 in Saskatchewan. The relationship between poor antipsychotic-taking behaviour and higher probability of hospitalisation in general [82] is congruent with reports of both increased any-cause mortality and relative excess of medical conditions that distinguish people with schizophrenia from the general population [162, 173, 188–194]. With regard to the mechanisms responsible for the link, it seems plausible to assume that adherence to antipsychotics may act as a marker of individual propensity to follow prescriptions from a physician in general and/or engage in correct healthy behaviour.

Poor medication adherence has also been reported in association with compulsory treatment and involuntary commitment [93, 115, 195–198]. A 2-year follow-up study of subjects with schizophrenia or other psychotic disorder consecutively admitted for the first time to the acute wards of Bordeaux psychiatric hospital reported a three times greater risk of compulsory readmissions in patients with poor medication adherence, defined as complete discontinuation of psychotropic medication against medical advice for at least 2 weeks over a 6-month interval [93]. Abnormally, high rates of compulsory treatments among poorly adherent patients with schizophrenia are likely to be at least partially mediated by the common association between this medication-taking behaviour and substance use, another well-established cause of compulsory treatments.

Overall, the clinical impact of adherence to antipsychotics on the risk of new hospitalisations is relevant; a regression analysis based on more than 4,000 patients with schizophrenia has shown how the odds for hospitalisation were lowered by a factor of 23 % in the presence of a 10 % improvement in MPR [60].

The effect of medication non-adherence on the risk of hospital admissions is likely direct, because a logistic regression analysis demonstrated that, even after controlling for others factors, “irregular medication use remained a significant and persistent predictor of rehospitalization”, as indicated by an adjusted OR of 1.99 [180].

Furthermore, the association between poor medication adherence and increased vulnerability to the revolving door phenomenon or, more broadly, rehospitalisation, seems to extend across different diagnostic categories [38, 101, 199–203].

With regard to the interval between the emergence of poor medication adherence and a new hospitalisation, it seems plausible to hypothesize a short time period [58, 60, 83, 90]. In particular, a cohort study of patients with schizophrenia in Maine and New Hampshire Medicaid who started therapy with second-generation antipsychotics supports this suggestion; the participants with a disruption in medication adherence had HRs of 1.54 and 1.77 for hospitalisation in the first

10 days of the gap in medication use, according to whether the admission was due to problems with general mental health or schizophrenia, respectively [83]. Gaps longer than 30 days have been shown to increase all-cause hospitalisations, that is, admissions related to medical or psychiatric conditions, with an HR of 1.57. Similarly, in a study of 4,325 California Medicaid patients with schizophrenia placed "on the more compliant end of the compliance continuum", the group with a maximum medication gap defined "as small as one to ten days in a one-year period" had almost doubled odds of mental health hospitalisation compared with the population who did not have gaps in medication therapy [60]. Furthermore, an Australian study based on consecutive hospitalisations or interventions from a 24-h community-based crisis team confirmed that a relevant number of readmissions among medication non-compliant patients occurred within the first 2 months after discharge [90].

At least two orders of indirect evidence further corroborate the conclusion that even a few days of poor medication adherence are sufficient to promote a new hospital admission. The re-emergence of psychotic symptoms after discontinuation of treatment with antipsychotics for any reason has been reported to occur in almost 50 % of cases within the first 2 months [25, 204] and the immediate postdischarge period has been associated with heightened risk for non-compliance [84, 85, 205, 206]. If it is true that very brief gaps in medication adherence may be sufficient to cause a rehospitalisation, it is also true [60] that the more the maximum gap in medication adherence increases, the more rehospitalisations occur. Therefore, the impact of poor adherence to antipsychotic medication on the risk of new hospital admissions seems regulated by a typical dose–effect relationship.

However, the negative influence of poor adherence to antipsychotics on hospitalisations is not restricted to an increase in the number of readmissions. It also involves longer duration of hospital stay [90, 115, 175, 179, 180, 184, 197, 207]. Gaps in the length of stay in hospital between adherent and non-adherent patients cannot be generalised. The phenomenon is highly dependent on the characteristics of the care system involved. The influence of medication adherence on the number of days spent in hospital is direct, because poor adherence remains the second best predictor of the length of rehospitalisation after controlling for other adherence factors [180]. From a quantitative perspective, the impact of adherence on the length of hospitalisation is likely to be not trivial, because a series of multivariate regressions performed with Medi-Cal data on 35,815 patients with schizophrenia showed that "the fraction of inpatient days attributable to not receiving antipsychotic medications was 13.1 %" [207].

As in the case of compulsory hospitalisations, substance abuse is a supplementary factor in the association between non-compliant status and increased risk for repeated readmissions and more occupied bed days [90]. For example, in patients with schizophrenia, schizoaffective disorder or schizophreniform disorder living within the Central Sydney catchment area and followed for 4 years, non-compliant individuals who abused substances had a 2-month interval between hospital readmissions, a value not far from the 4 months found among non-compliant subjects who did not abuse substances but 4.5 and 14 times shorter than

the intervals found for compliant patients who abused or did not abuse substances, respectively [90].

Adherent and non-adherent patients have also been reported to be different in relation to the use of other health care services. In particular, non-adherent individuals have been found to be higher users of emergency psychiatric services and acute wards [89, 90, 111], lower users of long-term rehabilitative beds [90] and have an increased rate of drop out from mental health clinics and day hospitals [111]. However, replication studies are needed for most of these issues.

Research Poor adherence to antipsychotics may have unfavourable consequences on schizophrenia research. When present but not adequately controlled, scarce medication-taking behaviour facilitates spurious results in clinical trials; this may produce a delay in registration and regulatory procedures, an unjustified premature cessation of research and development of new agents, a decrease in the incidence of adverse events with eventual preclusion of early recognition of important warnings, and inaccurate delimitation of the therapeutic dose range. Furthermore, interpersonal variability in adherence is a confounder in studies on markers and correlates of efficacy and tolerability of antipsychotic medications and weaknesses the power of statistical analyses, forcing the recruitment of larger sample populations.

Despite this long list, much of the current research includes only a rough measure of adherence: the pill count. This decision is based largely on a false perspective: the confidence that trial participants must be substantially adherent to the established medication regimen, because they have given their informed consent to enter the study.

Family and Significant Others Poor medication adherence promotes several negative consequences for the people who are close to the patient. Family members and significant others face an increased risk for violence and other illegal acts related to a psychotic recrudescence of the patient who has partially or totally discontinued antipsychotic medication. Individuals within the families of patients with schizophrenia who are poorly adherent are also frequently judged to be responsible for insufficient surveillance and, for this reason, they too are subjected to stigma. This blame for insufficient involvement is in sharp contrast with the evidence: the lives of the people close to poorly adherent patients are frequently beset by excess worry, distress and other negative emotional feelings, resulting in over involvement with supportive assistance and caregiving, and possible withdrawal from social contacts and employment difficulties.

Wider Society The clinical and behavioural effects of poor antipsychotic medication-taking behaviour in people with schizophrenia inevitably reverberate on society. This occurs through two main ways: the reinforcement of stigma attached to the disorder and its pharmacologic treatment and the increased susceptibility of the lay public to become victims of aggressive assault and other crimes committed by patients when they develop poor adherence.

Economic Consequences

The dramatic burden played by poor adherence to antipsychotic medication on patients, families, health care and justice systems, the community and wider society inevitably leads to substantial tangible and intangible costs. Despite the universality of this picture, extrapolation of costs outside the original context seems difficult to generalize, especially for absolute values of expenditure. A number of considerations contribute to this conclusion. For example, different countries guarantee different standards of care and supply services that are not comparable. Consequently, direct costs change on a nationwide basis according to the specific profile of the particular health care system. National effects also clearly operate in welfare, social assistance and justice systems. These national policies affect the economic burden for the patients and their families. Furthermore, expenditure can vary for some items over time. Changes in the price of medicines in relation to new more expensive drugs and substitution of older brand products with cheaper generics, the ongoing trend to reinforce community interventions and short-term hospital stays, and the pressure to guarantee new welfare and assistance standards are examples of how costs directly or indirectly attributable to schizophrenia can vary within this ever changing situation. These limitations inherent to the costs of schizophrenia also apply to the economic consequences of poor adherence to antipsychotic medications.

The literature on the cost of schizophrenia in general and poor adherence to antipsychotics in particular is frequently charged by another limitation: much of the evidence is derived from models that are highly conditioned by the set of postulates, assumptions and definitions used by different studies. For example, a 1995 study [122] found that, at the 1-year point, the relative contribution of non-compliance to rehospitalisation of "neuroleptic responsive, multi-episode … schizophrenia inpatients … discharged back to outpatient treatment" was approximately 32 %. Thirteen years later, another study [207] carried out by one of the authors of the previous report concluded that the annual "fraction of acute care inpatient admissions attributable to not receiving antipsychotic medications was 12.3 %" in subjects "who had received at least two outpatient or one inpatient claim for schizophrenia". Effects related to the time frame between the two studies may have contributed to the almost 20 % difference in the estimate of the re-hospitalisation rate due to poor medication adherence. Nevertheless, it seems unrealistic to assume that the interval between the two studies was the sole reason for the discrepancy in the results.

Other distinguishing features related to the design of the study must be hypothesised as being at least equally and possibly more important: differences in the sources of data collection, the clinical profile of the sample of reference, the definition of medication adherence, adjustments for the patients' background characteristics, the number and type of prerequisites and key assumptions to be satisfied, the levels of extrapolation required and the specific equations used should be taken into account. Key assumptions, in particular, are a crucial factor in

determining the results of economic simulation modelling studies because of their reliance on expert opinion rather than real practice. For example, by changing the scenarios within the simulation model, paroxetine has been reported to be more, equally, or less cost-effective than imipramine [208]. There is no reason to assume that a similar variability in the results does not apply in the case of economic comparisons of different antipsychotics or the adherence/non-adherence dichotomy.

Within the limits specifically imposed by these critical points, a number of general principles may be taken from the current literature [81, 122, 126, 174, 180, 207, 209–214].

First, "a definitive relationship exists between compliance and the economic costs of schizophrenia. Lower rates of compliance lead to higher costs of treating schizophrenia" [209].

Second, many relevant costs of illness cannot be easily quantified. Examples include the costs related to caregiving services provided by families, comorbid medical conditions, specific training and dedicated research. Therefore, the direct and indirect costs of schizophrenia, especially the latter, are systematically underestimated.

Third, because poor adherence to antipsychotic medication is a widespread phenomenon among people with schizophrenia and the direct medical costs per capita associated with this behaviour are relevant, it is not surprising that schizophrenia consumes a substantial share of medical expenditures [210, 213]. Despite its low prevalence, schizophrenia requires a large fraction of the funds allocated for the management of all mental illnesses in many health care systems [211, 213, 215–217]. The typical onset of schizophrenia in early adulthood and its lifelong and deteriorating course justify this burden. Considering that poor medication adherence apparently occurs at similar rates among patients affected by different mental disorders, its seems hard to qualify the relative redundancy of the direct costs of schizophrenia as a mere end product of the difficulties in taking antipsychotics according to the prescription of the treating physician.

Fourth, among the direct costs, the disproportionate consumption of resources accompanying poor medication adherence refers not only to costs related to psychiatric care but also to medical expenditure in general and involves the range of inpatient and outpatient services offered to individuals affected by schizophrenia. Therefore, interventions aimed at reducing the impact of poor adherence on the direct costs of schizophrenia require a global approach. Otherwise, the risk that decreases in expenditure for one item is counterbalanced by increase in others. Within this costly scenario, few doubts exist that "inpatient care constitutes the greater portion of direct medical costs for persons with severe mental illness" [180]. To get an immediate idea of the impact of medication-taking behaviour on the use of inpatient services, it may be enough to cite that "patients who failed to adhere to their medication regimen were over one-and-a-half times as likely as patients who did adhere to it to report use of in-patient services" [213]. However, non-adherence has also been shown to be "one of the most significant factors in increasing external service costs, by a factor of almost three" [213].

Fifth, inpatient expenditure related to poor medication adherence commonly identifies rehospitalisation as the most costly contributor. This persists even though continuous efforts are being made to externalize psychiatric care as much as possible. That rehospitalisation is a key cost-related item of inpatient services is well documented. For example, a study of schizophrenia Medicaid beneficiaries followed by San Diego County Adult Mental Health Services has found that "the hospital expenditures of those who were nonadherent were more than three times higher than the hospital expenditures of those who were adherent. The costs of those who were partially adherent or who had excess medication fills were about two and one-half times higher than the costs of those who were adherent" [81]. In a study carried out in Wisconsin involving patients with a severe form of schizophrenia or schizoaffective disorder, the hospital costs over a 12-month period were almost doubled among irregular medication users compared with regular users, US$3,421 and 1,799, respectively [180]. Therefore, the estimate [122] that 37 % of rehospitalisation costs incurred over 2 years by patients with schizophrenia were attributable to non-compliance seems plausible or even optimistic because, based on an incorrect a priori assumption, only the first rehospitalisation was considered, despite the fact that, in 1 year, many patients require multiple rehospitalisations in real-world practice [218].

Sixth, poor adherence to antipsychotics by patients with schizophrenia increases the likelihood of the need for external services [89, 90, 111, 126, 213] to the point that it has been reported to be the most significant factor responsible for increased direct costs unrelated to a stay in hospital [213].

Seventh, as emphasised earlier, many of the items typically included under the heading of indirect costs are unequivocally worsened by a poor medication adherence status. "Day-to-day care and support (of people with schizophrenia) is left to a great extent to family and friends, even if the patient does not reside with them" [219]. Furthermore, poorly adherent patients with schizophrenia present worsened functioning in almost all areas of daily living, have reduced life expectancy, develop a relevant loss of productivity due to disability, absenteeism, dismissal or unemployment, require increased use of welfare and assistance and incur justice problems more frequently. Despite this strong body of evidence, the issue of solid expenditure attributable to indirect costs related to poor adherence to antipsychotics continues to be substantially unanswered, even though indirect costs are a major fraction of the total economic burden of schizophrenia [215, 216, 220]. There is no reason to assume that this trend will be reversed for the items related to poor medication adherence. It seems reasonable to assume that indirect costs related to insufficient medication-taking behaviour may at least match the direct costs. The incontrovertible evidence that schizophrenia "is most prevalent during highly productive periods" of the vital cycle [215] makes these considerations easy to understand, and indirect costs are also at special risk for underestimation.

Eighth, direct and indirect costs attributable to violence, a possible secondary effect of non-adherence to antipsychotics, deserve separate consideration. Health care expenditure for offenders is not marginal because prisons are full of patients

who suffer from schizophrenia or other severe mental illnesses, and have a dual diagnosis of substance use disorder. This is an objective reality not necessarily related to the deinstitutionalisation process that could have fostered the "shift of persons with serious mental disorders from hospitals to criminal justice settings, a form of trans-institutionalization" [158]. Violent acts precipitated by non-adherence introduce patients into the justice system, and consequently a number of specific and expensive costs are incurred, such as police, civil and criminal courts, private and public defence lawyers, jail and prison. Furthermore, because "the potential for violence increases public fear, (and) prevents acceptance and inclusion of persons with psychiatric disabilities in society" [153], it follows that poor adherence to antipsychotics may lead to supplementary stigma. The economic consequences of this powerful reason for stigma remain in limbo as intangible costs.

Determinants and Moderators of Adherence to Antipsychotics

Non-adherence is often assumed a priori to be an irrational phenomenon [221]. Despite this premise, a comprehensive list of more than 200 variables as candidates related to medication adherence was drafted a quarter of century ago [222]. In addition, this highly diversified scenario has been progressively enriched over the years by supplementary items. Therefore, the term irrationality may extend beyond its literal meaning to explain the systematic, inevitable fiasco of attempts to reconcile medication-taking behaviour with single or few causal processes.

From a deterministic perspective, medication adherence must be regarded as a complex, multifactorial behaviour that expresses, at the phenotypic level, the result of a strong, dynamic flow of interrelations that occur systematically between numerous specific causal factors and several modifiable and unmodifiable superimposed moderators.

Both determinant and moderating factors are recognised as having multiple origins. Some are expressive of a preponderant involvement of the patient, the doctor, the medication or the system in general. Others are composite in nature in that they are simultaneously sustained by indissoluble interactions between variables of different origin. Furthermore, some variables apparently act as predictors of medication-taking behaviour, but they represent the sum of disparate contributors and do not have an appreciable direct effect on adherence.

Given these complexities, models devised to describe the mechanisms that govern the genesis of medication-taking behaviour (Fig. 7) are defective in origin since they represent an inevitable over simplification of what occurs in real life. Despite this, an analytical item-by-item discussion of different variables is useful for didactic purposes, provided by the reader always tries to reassemble the puzzle from a unitary perspective.

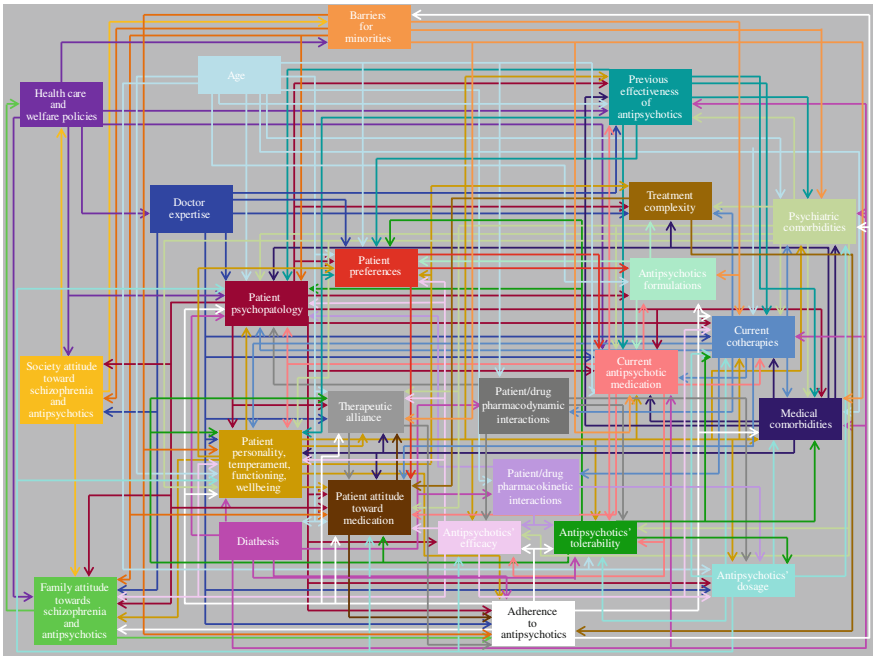

Fig. 7 Semplified, hypotetical model of contributors and moderators of adherence to antipsychotics in people with schizophrenia

System-Related Contributors

Many system factors are far from being neutral on medication adherence. Society and family constitute the areas of major interest, together with health care and welfare policies.

Wider Society Culture and acculturation, religion, ethic norms and value orientations, general social climate, tolerance and acceptance for minorities and diversities, economic trends, quality of information supplied by the media and reinforcements from testimonials contribute worldwide to steer the prejudices of society. This also applies to the case of stigma against severe mental illnesses, schizophrenia in particular and the use of antipsychotics for their treatment [223–229].

Although expression of a manifest stigma has probably relented in recent years, the phenomenon of "not in my backyard" remains widespread. It is therefore easy to understand why patients with schizophrenia have indicated stigma as the principal [230] or one of the most common [196, 231–233] barriers to regular use of antipsychotics. However, in an Australian study [234], patients with schizophrenia were able to recognize stigma but failed to associate the phenomenon with difficulties in taking the medicines as prescribed.

"Psychiatric stigma may be especially severe in some non-Western communities because of the meagre expenditure on mental health care, limited access to medical information, unpopularity of the human rights discourse, prohibitive risk of disclosure of psychiatric treatment and the paucity of advocacy work" [235].

Because stigma is a dynamic condition that can be controlled with dedicated interventions, numerous international, national and local campaigns on destigmatisation have taken place in recent years. In general, the programmes have been based on the hypothesis that improved knowledge on the biological foundation of schizophrenia should promote assimilation of the disorder with any other brain disease and thus improve medication adherence. Despite some experimental support [228], the assumption that correct knowledge about schizophrenia can exert anti-stigma effects has been found to be reasonable but unrealistic in practice. Several follow-up studies [223–225, 236, 237] have documented that, after biologically oriented educational interventions, an increased number of people effectively embrace the concept of schizophrenia as a physical disease but they do not reduce personal attitudes to stigmatize the disorder and the use of antipsychotics. For a better understanding of this gap, it may be useful to consider some evidence from a number of surveys [224, 226, 227, 229, 238] centred on the relationship between public beliefs on the causes of schizophrenia and social distance from the people affected by it. In particular, most of these reports stressed that a low attitude to judging schizophrenia as a real brain disorder rather than a largely volitional behaviour is a weak key to reducing prejudices about schizophrenia and its treatment, because this belief represents only one of the multiple contributors to stigma. Lay public sectors are also likely to be more susceptible to the detrimental influence of other aspects of schizophrenia such as the dangers, use of substances, scarce productivity, unpredictability, impulsivity and perceived differences in communication modalities. In addition, discoveries on the biological correlates of schizophrenia, in particularly those related to molecular genetics and brain imaging, may sometimes be counterproductive because they erroneously lead to stigma. Translation from improved cultural disposition to concrete behaviour needs a long time.

Family and Significant Others The influence of families and, more broadly, significant others on medication-taking behaviour of patients with schizophrenia is well acknowledged since the advent of neuroleptics. A 1963 report [31] emphasised, for example, that "patients whose drug taking was supervised by a member of the household were much more likely to take the drugs regularly".

Several contributing factors may be involved in driving the relationship. The attitude of society towards schizophrenia and its treatment certainly play a crucial role. In general, the position of proximity to patients suggests that messages filtered by those close to the patient should be more penetrating. However, it must also be taken into account that the inevitable relationship with the affected person is associated with better acceptance of the disorder and the use of antipsychotic agents [229, 239]. This implies that the eventual stigmatising atmosphere of the community is more likely to be dampened rather than potentiated by significant

others. Nevertheless, when individuals close to the patient become the object of societal preconceptions or are entrenched in coarsely obscurantist positions, they may be inclined to amplify or generate further stigma, thus contributing to the poor medication-taking behaviour of the patient.

Together with stigma and prejudices, distress, emotional distance, ambivalence and difficulties staying close to the affected person are common supplementary obstacles to reminding, supervising and persuading patients to take medications as prescribed. ([31, 81, 91, 111, 196, 231, 240–248]; for supplementary references, see [38, 47, 64, 98, 214]). Reports that direct supervision in residential treatment settings, living in supervised housing and consistent attendance at self-help meetings [249, 250] have a positive influence on medication adherence of people with schizophrenia may be seen as further indirect proof of the relevance that significant others assume in favour of correct medication-taking behaviour of patients living at home. The same applies to the demonstration that "multifamily group therapy specifically tailored to improve medication adherence is associated with improved outcome" [251].

Health Care and Welfare Policies Funding and the rules of the system are established by health care policies. Health care policies pursued in different countries therefore have a strong effect on medication-taking behaviour. This influence is largely mediated by indirect effects related, in particular, to the minimum levels of guaranteed care, the intensity and quality of vocational training provided to members of the treatment team and the planning of educational campaigns addressed to patients, their families and the lay public. All these items affect relevant moderators of adherence behaviour, such as the competence of the personnel operating within the system, the patient–doctor relationship, shared decision making and stigma.

However, by imposing governance on accessibility to therapies, health care policies exert a direct driving force on a patient's inclination to take medicines as prescribed. The pressing need for rigorous cost containment in response to escalation of the price of drugs and the concomitant funding shortfalls related to the worldwide economic crisis have promoted the adoption of a large series of ad hoc strategies that could potentially have a negative impact on medication-taking behaviour. Preferred drug lists, tighter formularies, priority use of generics, exclusion of some pharmacologic classes from reimbursement, medication algorithms, mandatory authorisation before reimbursement, limits to the number of prescriptions that may be filled without previous authorisation and forced cost-sharing belong to this list.

In general, restrictive policies that have resulted in cost savings have often been accompanied by unintended negative secondary effects, such as deterioration in medication adherence [252]. Because non-adherence is especially important for essential therapies and in the presence of chronic disabling illnesses [253, 254], schizophrenia and antipsychotics are ideal acid tests for challenging the direct impact of restrictive policies on medication adherence. Overall, the sequence that links cost-containment policies, particularly the need for a fee, with loss of

medication adherence in patients with schizophrenia has received experimental support. For example, during the era of first-generation antipsychotics, there was a 15.4 % decrease in the use of this class of medications among New Hampshire Medicaid patients after the introduction of the limit for reimbursement to three prescriptions [255]. This decrease was even bigger, 21.2 %, for regular recipients, and after the discontinuation of the policy, the use of medication "rose to a level slightly above pre-cap rates". The same study has also shown how, in New Jersey, a state that refused to lay down limits on drug reimbursement, patients did not change their level of medication use during the same period. Similar results have been reported more recently, after the advent of second-generation antipsychotics, in comparisons of data related to Mississippi, Indiana and Minnesota [256], three states characterised by remarkable differences in relation to cost-containment policies: Mississippi has imposed "a cap on the number of drugs reimbursable per enrollee at seven prescriptions per month with a prior authorisation requirement for monthly dispensations of more than five prescriptions, an increase in copayments for brand name medications from $1 to $3 per fill, a mandate to dispense generic medications when available, and a 34-day restriction on the days supply filled per prescription"; Indiana and Minnesota have adopted more lenient cost-containment strategies. The consequence for medication adherence has been that "patients in Mississippi were 4.9 % less compliant with antipsychotic treatments and experienced 20.5 % more 90 day antipsychotic treatment gaps" than patients in Indiana and Minnesota.

Patients harried by cost-containment interventions cut their therapies on the basis of disease-related and drug-related preferences. In a large-scale study of VA patients with schizophrenia [254], medication co-payment was found to be associated with an appreciable decline, nearly 25 %, in refills for psychotropic agents but not for other medicines.

Loss of medication adherence in response to the adoption of restrictive policies may be well reconciled with the hypothesis, typical of the Health Belief Model, that the need for a co-payment and difficulties with access to medicines may tip the balance in individuals with an already fragile medication-taking behaviour in favour of an excess of disadvantages over benefits. Furthermore, extra expenditure may sometimes be literally unaffordable, for example, in the case of most indigent patients. Reports indicating an association between poor adherence to antipsychotics and unemployment, financial obstacles, low occupational status, low parental class, homeless condition, lack of welfare or access to transfer payment add weight to this situation ([19, 79, 81, 93, 111, 147, 159, 187, 231, 257–260]; for supplementary references, see [64, 98, 214]). On the other hand, patients with schizophrenia have been reported [230] to perceive homelessness and lack of social support among the principal barriers to their adherence to antipsychotics.

Doctor-Related Contributors

Within the background defined by the levels of assistance and treatment contingently supplied by the health care system of reference, the specific competence and ability of the physician in the areas of psychopathology, general medicine, clinical psychopharmacology and maintenance of interpersonal relationships play an essential role in the patient's inclination to follow medical advice.

Psychopathologic Expertise Mistakes in psychiatric diagnosis and recognition of defined domains of psychopathology activate a cascade of events that reverberate negatively on medication adherence. Scarce psychopathologic expertise increases the probability of unsuccessful treatment and this, in turn, leads to unjustified use of polypharmacy and high medication doses, with the risk of an excess of adverse events and a drop in expectations towards psychopharmacotherapies. These factors enter a number of pathways leading to poor medication-taking behaviour.

Medical Expertise People with schizophrenia have an excess of medical comorbidities and vulnerabilities linked, in particular, to unhealthy lifestyles, shared diathesis, psychopathologic traits facilitating denial or poor interest in physical health and care inequalities. In the absence of the necessary medical expertise, the treating physician risks exposing patients with schizophrenia to a disproportionate number of iatrogenic health effects directly related to the individual medical history, leading to probable induction of poorer medication-taking behaviour.

Psychopharmacologic Expertise The expertise of the physician in clinical psychopharmacology interferes at multiple levels with adherence to antipsychotics. In particular, detailed knowledge of the efficacy, tolerability, pharmacokinetics and pharmacodynamics of the various antipsychotics is essential to tailor individualised pharmacotherapies to maximize the chances of improvement and minimize the risk of adverse events, two basic components for good adherence. Also the doctor's competence in gathering information from the patient's psychopharmacologic history is essential for individualised interventions.

Another important issue for medication-taking behaviour that requires the competence and attention of the physician refers to the use of polypharmacy, a phenomenon that is in use worldwide and is expanding [7, 80, 81, 261–278]. A large-scale study [274] on office-based psychiatry over the 10 years straddling the turn of the millennium has quantified the extent and evolution of this phenomenon. The trial showed that "visits with two or more medications increased from 42.6 % in 1996–1997 to 59.8 % in 2005–2006" and that during the same time period "visits with three or more medications increased from 16.9 % to 33.2 %". The same study has also shown that a diagnosis of schizophrenia was associated with higher odds of receiving not only two or more antipsychotics but also combinations of agents of this class with antidepressants, mood stabilizers and sedative

hypnotics. Increased pressure to search for greater and faster improvements, low levels of expertise in drug–drug interactions, the ability to recognize psychiatric comorbidities and renewed popularity of the dimensional approach to clinical psychopharmacology are some of the major factors supporting the use of polypharmacy in clinical routine. Polypharmacy is sometimes indicated. More commonly, however, patients are prescribed medication combinations in the absence not only of acceptable experimental support and specific endorsements but also despite common recommendations to use co-therapies as a last resort [272–274, 276–279] because, "while the evidence for added benefit of antipsychotic polypharmacy is limited, there is growing evidence regarding the increased adverse effects associated with such combinations" [274]. This call for caution is recommended based on meta-analytic evidence of the effects of polypharmacy on the efficacy and tolerability of antipsychotics [275, 280] and the probability of publication bias related to the confinement of efficacy data to studies carried out in China or other Asian countries [280]. Therefore, the statements [281] that "seldom can such polypharmacy be considered rational or scientific" and "on the contrary, it is indicative of a serious gap between a basic knowledge of drugs and their clinical use" seem fully relevant today.

Irrespective of whether polypharmacy is correct or not, it is a contributing factor for poor medication adherence, because it promotes dosing complexity and increases the incidence of adverse events. In confirmation of this, it may be enough to emphasize that in a representative sample of Florida Medicaid beneficiaries [210] "a status of limited to negligible adherence occurred at rates of 18.6, 28.4 and 37.8 % among patients treated with atypicals, typicals, or typical plus atypical, respectively".

Relational Expertise When the other skills and expertise of the physicians are equal, the ability to promote and maintain a trusting, collaborative patient–doctor relationship has an appreciable influence on adherence to antipsychotics, because this attitude represents a basic principle for therapeutic alliance and shared decisions.

Patient-Related Contributors

The group of mainly patient-related determinants and moderators of medication adherence include numerous factors, in particular premorbid functioning, well-being, symptoms of psychosis, co-presence of depression, cognitive functioning, insight, psychiatric and physical comorbidities and genetics. Some of the contributors have been extensively analysed, whereas others have seldom been challenged.

Premorbid Functioning and Wellbeing Premorbid functioning and wellbeing belong to the group of candidate contributors to antipsychotics that have been the subject of sporadic interest so far.

With regard to premorbid functioning, in a report on 186 patients with a first episode of a schizophrenia spectrum disorder admitted to the Calgary Early Psychosis Programme, an association between good functioning and future good adherence has been reported [91]. Similar results have been found in a cohort of patients with a first-episode of psychosis admitted to the EPPIC of Melbourne [97]. This promising finding, however, is in contrast to some negative results [19, 93, 246]. Thus, it seems reasonable to assume, at least contingently, that the influence of premorbid functioning on adherence to antipsychotics is small, if any.

The issue of an eventual influence of personality and temperament on medication adherence has been almost ignored. However, current evidence is at least suggestive of some relationship. High sensation seeking, disinhibition and susceptibility to boredom have been associated with poor adherence in a mixed group of patients with psychosis or mood disorder [282]. Furthermore, in patients with schizophrenia, medication adherence has been reported to be inversely related to self-directness and novelty seeking, a concept close to sensation seeking [283]. A negative impact on medication-taking behaviour has also been reported for high agreeableness, another personality trait [284].

The weight exerted by wellbeing and functioning on the probability that patients will follow the prescriptions of the treating physician as indicated are more robust. A discrete number of reports emphasize that, with few exceptions, there is a positive association between wellbeing and functioning and medication adherence ([19, 59, 88, 91, 185, 249, 258, 285–288]; for supplementary references, see [64]). In particular, a subanalysis of the SOHO study [59] estimated that a 25 % improvement in SWN-k total and self-control scores was associated with higher ORs, 1.22 and 1.25, of being compliant. A longitudinal observation [88] on 162 patients in ambulatory treatment for psychotic disorders estimated an almost 5 % reduction in the risk of non-adherence for every one-point increase in WAI or GAF score.

Psychotic Symptoms Undoubtedly, there is an association between adherence to antipsychotics and symptom severity in patients with schizophrenia. However, as repeatedly underlined, the relationship is bidirectional and the possibility of disentangling the moderating effect of medication adherence on the clinical picture and the other variables is often impossible because of the difficulties in identifying which variable comes first.

Despite this inherent limitation and the presence of conflicting results, the working hypothesis that the greater the severity of psychotic symptoms, the less the medication adherence seems well supported ([31, 51, 59, 89, 91–94, 96, 97, 111–113, 117, 125, 127, 181, 185, 186, 197, 205, 213, 243, 248, 250, 258–260, 284, 286, 287, 289–305]; for supplementary references, see [38, 47, 64, 98, 214]). The association, however, was based on different variables, such as global

severity, severity of some definite psychopathologic domain, the positive in particular, or severity of defined symptoms, more frequently those pertaining to the area of delusional ideation.

Psychotic symptoms contribute to medication adherence in patients with both first-episode and chronic schizophrenia and have a modest power. For example, in a group of patients first admitted with schizophrenia or another psychosis, who were evaluated with the PANSS, "the likelihood to present with poor medication adherence was 1.6 greater for each one-point increase on the item delusion, and 1.5 times greater for each one-point increase in the item suspiciousness" [93].

Depressive Symptoms The presence of depressive symptoms has been associated with poor medication adherence in such disparate disorders as cardiovascular disease, diabetes and hepatitis C [306–308]. People with schizophrenia are not immune to this general trend. A number of reports ([19, 94, 117, 137, 186, 287, 309–311]; for supplementary references, see [47]) that have explicitly tested the issue in patients with schizophrenia have concluded, with some exceptions, that there is an inverse relationship between depressive symptoms and adherence to antipsychotics. Furthermore, in a large-scale, 3-year, prospective, naturalistic follow-up of patients with schizophrenia included in the US-SCAP [51], previous treatment with antidepressants ranked fourth among the most powerful predictors of non-adherence: this result gives further indirect support to this negative correlation, because the prescription of antidepressants may be considered a rough proxy of a depressive condition. An opposite conclusion is suggested by the observation [290] from a small sample of first-episode patients that patients with schizoaffective disorders had higher rates of compliance compared with individuals affected by schizophrenia.

Cognitive Functioning Some studies have explicitly tested whether cognitive function has an influence on adherence to antipsychotic medication in patients with schizophrenia ([19, 51, 67, 137, 232, 241, 289, 295, 312–315]; for supplementary references, see [38, 47, 64, 98]). Although studies vary as to the measures used, referral to global or partial aspects of cognitive functioning and some conclusions, the emerging overall picture is that cognitive dysfunction merits a mention among the contributors to poor adherence. Three large-scale trials seem particularly representative. In a German compliance survey [67] of 5,729 patients with schizophrenia, the treating psychiatrists mentioned the need for some external help to remind patients to take medicines and the presence of problems related to cognitive deterioration among the most frequent patient-related contributors of poor adherence, with frequencies of 61.8 and 54.9 %, respectively. A second trial [233] involving 2,824 Korean patients with schizophrenia treated by 131 psychiatrists concluded that 83 % of the sample "needed help from someone to remind … to take medication daily". Similarly, the third trial, a prospective observational US study of 1,579 patients with schizophrenia treated in usual care settings [51], placed patient-reported cognitive impairment first within a list of 39 of the leading predictors of medication adherence. The observation [19] that patients with first-episode

schizophrenia who stopped antipsychotics against medical advice "had poorer estimated premorbid cognitive ability than patients who consistently took medication" may be interpreted as a further indication of the negative impact of impaired cognition on medication-taking behaviour.

However, evidence of an association between higher cognitive performance and poor medication adherence has also been reported [137]. This finding is mirrored by the observation [312] that "increasing neurocognitive impairment was associated with more positive self-reports of medication adherence". The association between neurocognitive impairment and a valid adherence status is probably spurious resulting from the propensity of patients with cognitive deficits to over report their adherence; when the judgement of a significant other was used to define individual medication-taking behaviour, the apparent beneficial influence of cognitive impairment on medication adherence disappeared [312].

Insight Despite the persistence of some controversy about the composite nature of the phenomenon, insight does include a psychotic factor when it expresses a distortion of the reality process. Insight goes beyond this distinctive dimension when it depends on other contributing factors, for example, neurocognitive functioning, cultural and educational background and confrontation with testimonials. For this reason, the relationship between medication adherence and insight merits further analysis.

The available literature is substantial and supports, with some exceptions, the conclusion that insight or at least some of its major components are to be viewed as directly associated with medication adherence ([91, 92, 94, 97, 111, 113, 114, 137, 185, 186, 196, 231–233, 241, 244–246, 248, 259, 284, 286, 289–292, 294–296, 302, 312, 313, 316–327]; for supplementary references, see [38, 47, 64, 98, 214]). In a national survey of psychiatrists engaged in the management of schizophrenia, the indication that "denial of illness was the most commonly cited primary reason for antipsychotic nonadherence" [328] gives further weight to the relevance of insight in medication adherence.

The strength of the impact of insight on individual levels of medication-taking behaviour is not well established due to the relatively small size of the samples recruited in most of the studies and the presence of specific confounders. For example, some patients present too much insight and this feature is not an indicator of good medication adherence but, rather, suggests the opposite [330]. Another inherent confounder refers to the common entry of perceived need for treatment among the items that measure medication adherence; this choice implies that "examining the impact of such a component on adherence may be seen as tautological" [92]. However, the difference between asserted and actual adherence is likely to reduce the distortive consequences of this methodological bias [330–332].

The positive link between insight and adherence does not seem to be confined to some of the specific measures of insight used in different studies and may be indifferently applied to patients with both first episode and chronic schizophrenia.

The observation [317] that improvement in insight goes hand in hand with improvement in compliance should be viewed as further validation of the

interrelatedness between the two phenomena and a strong indication in favour of the use of insight-oriented interventions to improve adherence to antipsychotics in patients with schizophrenia who manifest poor insight and fail to take therapies as prescribed. In addition, the demonstration of an inverse association between adherence to antipsychotics and denial coping may be considered as a rough example of the detrimental influence played by poor insight on medication-taking behaviour because "impaired insight and the employment of denial coping strategies have been found to be related but distinct characteristics" [300].

Psychiatric Comorbidities Substance use disorders are a major topic in the current literature on the association between adherence to antipsychotics and psychiatric comorbidities ([51, 79, 81, 88, 90–94, 96, 97, 111, 113, 127, 137, 182, 185, 187, 205, 207, 210, 213, 244, 258, 284, 285, 293, 297, 333–335]; for supplementary references, see [38, 47, 64, 98, 214]). Overall, convergent evidence indicates that substances have an appreciable negative influence on the extent to which patients with schizophrenia follow the pharmacologic prescriptions of their physicians. However, as emphasised earlier, the association is bidirectional and thus at risk for a vicious circle of reciprocal reinforcements.

Because the few studies that have failed to document an association have mostly considered substance use disorders according to a lifetime or historical perspective [92, 93, 117, 259, 333], it seems reasonable to hypothesize that the link with poor medication adherence depends on a number of non-mutually exclusive pathways related to the recent use of substances. Within this perspective, impairment of judgement, exacerbation of psychotic symptoms, decline of motivation to pursue long-term goals, devaluation of the beneficial effect of antipsychotics, paradoxical fear of complications related to the substance–antipsychotic mixture, increased risk for conflicts with supportive figures, erosion of social support and distress secondary to the emergence of adverse events typical of exposure to substances are among the most obvious contributors. An appreciable role must also be attributed to increased risk for dosing complexity due to the need for polypharmacy. Demonstration [336] that psychoactive substances enhance extrapyramidal symptoms supports a supplementary alternative hypothesis based on the induction of increased emergence of these and, possibly, other adverse events typical of exposure to antipsychotics.

Whether the negative impact of comorbid substance use disorders on the medication-taking behaviour of people with schizophrenia is at least the representative of a generalised trans-diagnostic association between poor adherence to antipsychotics and a comorbid status remains largely unanswered because of scarce and contrasting evidence. For example, a study [337] of Medical outpatients with schizophrenia "who initiated monotherapy with a conventional or atypical antipsychotic medication" has reported that an additional diagnosis of bipolar disorder was "associated with a significantly lower rate of persistence" with the treatment. At the same time, however, a past psychiatric disorder other than substance use disorder has been associated with slightly less risk of the patients "to become medication refusers as opposed to nonadherent patients"[97].

Medical Comorbidities People with schizophrenia are at increased risk not only for psychiatric but also for medical comorbidities [162, 173, 188–192, 194]. Patients with schizophrenia may not pay due attention to medical problems because they ascribe their physical symptoms to the mental disorder, generalize illness denial typical of schizophrenia to concomitant medical conditions, are scarcely involved in personal physical problems because of the overwhelming pressure of psychotic symptoms or, more simply, present deficits of cognitive flexibility and memory that prevent them from following medical advice. In addition, persistent unhealthy lifestyles that predispose them to medical conditions are commonly observed in concomitance with schizophrenia [338–340]. Unhealthy lifestyles and defined medical conditions found in individuals with schizophrenia may also depend on specific familial, possibly genetic, predisposing factors [338, 341–345]. Furthermore, the families, urged by the psychosis of the affected relative, may give insufficient attention to somatic problems, avoid intervening on unhealthy lifestyles and refuse to participate actively in the processes of care. Physicians and the health care system in general also contribute to the poor physical health of patients with schizophrenia. For example, it is common that psychiatrists have inadequate expertise to treat medical problems and general practitioners and specialists in other branches of medicines are insufficiently trained to work with patients affected by a severe mental illness. In addition, services that are not sufficiently tailored to the needs of people with schizophrenia may create barriers to patients receiving a good standard of medical care.

Multiple pathways contribute to increase the risk that patients with schizophrenia are not only undiagnosed or untreated for their medical comorbidities but also receive inequality of care [192, 346–355].

Irrespective of the participation of the various contributors, medical comorbidities interfere negatively with adherence to antipsychotic medications. This inverse relationship depends largely on the almost inevitable use of polypharmacotherapies. Polypharmacotherapy makes the medication regimens more complex, may facilitate drug–drug interactions that interfere with the pharmacokinetic and/or pharmacodynamic profile of the antipsychotic, and increases the chances of more frequent and more severe adverse events.

The therapies prescribed for comorbid medical comorbidities have also been reported to be at a higher risk for poor adherence compared with antipsychotics [102]. If confirmed, this could lead to a vicious circle whereby poor adherence worsens the prognosis of the medical comorbidity, the poor prognosis of the medical comorbidity forces more aggressive interventions, and the more aggressive medical interventions exert a further negative impact on adherence to medications in general and antipsychotics in particular.

Genetics Many lines of evidence from descriptive and molecular genetics make the assumption that a number of factors that shape medication adherence have a relevant contribution from genes no less refutable. The psychopathologic domains of schizophrenia, drug metabolism and effectiveness of antipsychotics have

sufficient in-depth genetic expertise [70, 72, 356–362]. Despite the strength of the construct, no study has so far tried to control for genetic variance in the influence of those contributors of medication adherence that have a genetic component. Therefore, any discussion on this topic remains purely unsubstantiated.

Furthermore, at a purely theoretic level, it cannot be excluded that genetics or, better, epigenetics affect medication-taking behaviour not only for some disease-specific or drug-specific contributors but also individual proneness to follow medical and health advice in general.

Drug-Related Contributors

Among the principal drug-related factors that define the individual levels of medication adherence, the differences between antipsychotics, effectiveness, dosing complexity and dosing regimens have been topics of major interest.

Differences Between Antipsychotics After the advent of second-generation antipsychotics, it was hoped that they would improve the prognosis of schizophrenia and promote a more valid medication adherence due to their alleged improved efficacy/tolerability profiles compared with conventional antipsychotics [363]. Overall, controlled clinical trials, meta-analyses, guidelines and extensive use in practice have confirmed that many of the new antipsychotics are first-line options for the management of people with schizophrenia. Nevertheless, it is also true that second-generation antipsychotics are far from being ideal and that differences between individual agents do occur [6, 7, 9, 14–17, 364].

Despite the sound premise, the contribution of second-generation antipsychotics to the process of adherence improvement has been less striking than supposed ([61, 80, 81, 88, 94, 110, 111, 137, 153, 210, 248, 249, 285, 295, 337, 365–378]; for supplementary references, see [38, 64]). Three main lines of evidence support this conclusion. First, a non-marginal minority of comparisons between conventional and atypical agents has not corroborated the initial working hypothesis. Second, even when documented, the advantage of novel antipsychotics compared with first-generation agents has been shown to be small to moderate. Third, high numbers of patients with schizophrenia treated with second-generation antipsychotics continue to deviate from the prescriptions of their physicians. This scenario is not surprising, because the hypothesis that the entry of atypicals onto the market could be the keystone to overcome the problem of medication adherence in schizophrenia appears overly naive. The multifactorial origin of this treatment behaviour excludes a priori the possibility of an overwhelming contribution played by a single factor. Furthermore, comparisons of medication adherence involving patients treated naturalistically with different agents are at risk for selection effects related to an initial preference for one class of antipsychotics over another. In particular, in health care systems that encourage initial use of cheaper medications, patients who stay with first-generation antipsychotics should be

inherently at higher likelihood for good adherence than individuals switched to an atypical agent. In addition, whenever first-line use of novel antipsychotics is promoted, the indication to switch to a conventional agent will presumably involve patient populations with an excess of cases with poor adherence. Selection effects may also be working in comparisons of medication adherence that involve clozapine, given its uniquely restricted indication. One of the largest studies on adherence to antipsychotics carried out to date [80] supports the relevance of selection effects in the daily routine. Compared with the group of 25,931 individuals exposed to a conventional antipsychotic in monotherapy, the sample of 23,702 patients treated with an atypical agent included only a 3.7 % excess of cases with an MPR value less than the 0.8 cut-off used to identify poorly adherent individuals. Despite the demonstration of a preferential link between first-generation antipsychotics and good medication adherence, patients on clozapine had higher MPR values compared with patients treated with conventional or other atypical agents [80]. Furthermore, among patients switched from a typical to an atypical agent, the percentage with poor adherence dropped from 46 to 40 %. In contrast, among patients switched from a new to an old antipsychotic medication, the percentage of poorly adherent individuals increased from 49 to 64 %. In turn, in a large sample of patients with schizophrenia starting on a second-generation antipsychotic, patients who had previously been exposed to a conventional agent persisted and complied better with the atypicals [79]; this indirectly supports the idea that novel antipsychotics are perceived to be better than conventional agents in relation to the issue of medication adherence.

The possibility of a differential effect played by individual antipsychotics on medication adherence has also been challenged through comparisons between agents of the same class. However, head-to-head comparisons between first-generation antipsychotics are scant ([66, 197, 379]; for supplementary references, see [64]). A 1971 report [379] from the Walter Reed General Hospital at Washington found that "more outpatients on thioridazine, 55 %, than on chlorpromazine, 15 %, were not taking minimal amounts of medication", a rather surprising finding, in light of the demonstrated lower incidence of side effects "with thioridazine and the widely held notion that patients are more likely to take a drug having fewer side effects". A report from a VA mental hygiene clinic [66] speaks in favour of some drug-specific effect played by first-generation antipsychotics on medication-taking behaviour: apart from 3–10 % of refusers who would not take medications at all, patients on chlorpromazine, thioridazine, trifluoperazine and perphenazine "were judged to be taking significantly less than the amount prescribed" in 20, 35, 10 and 12 % of cases, respectively. However, evidence also exists that, among acute inpatients, refusers and nonrefusers do not differ regarding the type "of described neuroleptic medications" [197].

Intraclass comparisons between second-generation antipsychotics are more common. The results, however, are conflicting [61, 79–81, 88, 110, 137, 152, 305, 365–368, 373, 375–378, 380–385]. Reports indicating that one medication is better than another in terms of good adherence rates are almost systematically at variance with others that fail to demonstrate any difference or, even, draw opposite

conclusions. This may be explained by assuming an active role for a number of confounders. Two seem to merit particular mention. One refers to the common presence of a study sponsor. The other comes from the observation that in the decisional process in the real world, a pre-ordered ranking of preferences is typically adopted for the selection of the first-choice medication and this inevitably generates selection effects.

Although the various independent studies lack univocal results and frequently present appreciable points of weakness, it seems reasonable to conclude that second-generation antipsychotics should be weakly preferred to conventional agents in order to improve medication adherence. Within this specific perspective, however, none of the novel antipsychotics may be definitively considered more convenient than another, with the reasonable exception of clozapine in resistant patients.

Efficacy and Tolerability Among the two main components of effectiveness, efficacy and tolerability, the former has so far received only marginal interest in studies that aim to challenge the putative contributors of adherence to antipsychotics. As intuitively predicted, the emerging evidence [59, 94, 137, 139, 231, 285, 386] speaks in favour of the fact that a poor response and no perceived benefits call for non-adherence and, on the contrary, a good response calls for adherence.

Attempts to establish a relationship between adverse events induced by antipsychotics and medication-taking behaviour are more common, although the decision to give preference to adverse events is somewhat surprising considering that the recognised benefits of medications have been reported to have more influence on adherence than adverse events [246]. In confirmation of this, a post hoc pooled analysis [387] of 866 patients with schizophrenia or related disorder who discontinued treatment in four randomised clinical trials has reported that "the most common reason for early discontinuation was poor response/psychiatric symptom worsening, which was three times the rate of patient discontinuation due to medication intolerability".

Despite the presence of a discrete number of negative or even opposite results, retrospective, cross-sectional and prospective studies suggest overall that medication-taking behaviour is unfavourably affected by the patient's present or past negative experiences in relation to the tolerability of antipsychotic medications ([19, 30, 31, 51, 59, 92, 94, 110, 111, 113, 139, 181, 197, 205, 231, 234, 241, 244, 246, 258, 285, 286, 289, 294–296, 302, 309, 310, 324,325 368, 374, 388–394]; for supplementary references, see [38, 47, 64, 98, 214]). The relatively lower benefit of compliance therapy observed among patients with extrapyramidal symptoms support this conclusion [317, 324, 392].

Harmful side effects such as akathisia, tremor and other extrapyramidal disturbances have negative effects on medication-taking behaviour. However, the association mainly involves those events that, irrespective of their objective severity, induce levels of subjective distress that are intrusive, scarcely acceptable or have a negative impact on quality of life and self-esteem. Among these are

sedation, weight gain, sexual dysfunction, galactorrhea and some anticholinergic disturbances. Subjective distress due to side effects fluctuates over time [395] and is influenced by factors that, aside from the mere pharmacologic perspective, involve personal expectations, past experiences, trust in alternative therapeutic options, opinions of significant others, competence of the clinician in explaining and managing adverse events and fear of stigmatisation because some adverse event may explicitly indicate the use of an antipsychotic [395, 396]. The influence of non-pharmacologic contributors explains why subjective distress has sometimes been reported to be unrelated to objective records of adverse events and is especially difficult for clinicians to recognize and quantify [395]. Furthermore, the burden of distress due to side effects seems to be estimated differently by doctors and patients [397] and this constitutes a further relevant complication for precise definition of the involvement of distress in the genesis of poor medication-taking behaviour.

The subjective report seems to be "a much more relevant predictor of non-compliance than objective measures" [395] and this statement fits well with the observation that many patients cite side effects among the primary reasons for non-adherence or stopping the therapy [197, 230, 388].

From a critical perspective, it must be also stressed that a split approach to the effects played by the efficacy and the tolerability of antipsychotics on medication-taking behaviour is incorrect to some degree, because people taking medicines are not inclined to see side effects and symptom improvement as separate issues [398].

Treatment Complexity The influence of treatment complexity on patient adherence to prescribed medications has been a subject of intensive investigation over the years in studies focused on dosing frequency and prescription of polypharmacy for a variety of illnesses and pharmacologic classes, schizophrenia and antipsychotics included ([29, 40, 42, 55, 79, 80, 100, 103, 110, 112, 240, 241, 249, 281, 297, 334, 374, 399–404]; for supplementary references, see [47, 64, 98, 214]). Apart from some results that swim against the tide, the overall emerging key conclusion is that the general principle of simplicity results in good adherence: indeed, the rule the lower the frequency of dosing, the higher the medication adherence seems to be sufficiently supported. Nevertheless, a non-negligible number of patients treated once a day, in clinical practice, continue "to have imperfect dosing" [42]. However, this finding is not surprising because, as already emphasised, medication-taking behaviour has a multifactorial origin and consequently single variables may explain only a small proportion of variance.

The influence of dosing complexity on adherence is affected by medication type and the common presence of other second-order associations. A VA study [334] involving more than 35,000 patients with schizophrenia or schizoaffective disorder who were prescribed one oral antipsychotic medication and filled at least one outpatient pharmacy prescription is paradigmatic of the intricate nature of the link between dosing frequency and medication adherence. In the group of 1,639 patients treated with a once-daily dose initially and then incurred an increase in their total dose, those who also increased the dosing frequency developed a

relative adherence loss compared with individuals who remained on once-daily dosing after the increase. The 1,370 patients who had a decrease in dosing frequency from more than once-daily to once-daily had superior MPRs compared with patients without a decrease in dosing frequency. Among the 32,612 patients who remained on a consistent frequency, no difference in MPR emerged between individuals originally prescribed a once-daily dose and those treated more than once daily, even though in the multivariate analysis "more than once-daily dosing frequency was weakly associated with poor adherence" [334].

Whether the number of daily doses is also inversely associated with the appropriateness of taking medicines within the prescribed time frame [100] remains an open question.

The fact that patients with schizophrenia have ranked difficulties with the regimen in ninth position among the major barriers to taking antipsychotics as prescribed [230] further supports that dosing complexity has practical relevance in defining the individual level of medication adherence.

Clearly, although all the literature has so far focused on dosing frequency, other indicators of complexity may also affect medication-taking behaviour. The requirement to take drugs before food or other restrictive dosing regimens are some of the most obvious examples that should be investigated.

Antipsychotic Dose The current literature on the putative effects of the antipsychotic dose on medication-taking behaviour is far from being conclusive ([79, 80, 111, 117, 197, 288, 291, 295, 309, 320, 365, 405]; for supplementary references, see [47, 64]). Reports indicating an association between poor adherence and high doses are at odds with others that have failed to demonstrate any appreciable dose effect or have documented that poorly adherent individuals are at lower risk for having ever received a high antipsychotic dose.

These discrepancies may be reasonably justified considering that the influence of medication dose on adherence is largely sustained by second-order associations and spurious contamination. It is true, for example, that a low dose of an antipsychotic agent may favour adherence, reducing the potential for adverse events, but it is also true that this pro-adherence effect frequently occurs at the detriment of efficacy, another adherence promoter. In clinical routine, the prescription of high doses of antipsychotics is also commonly coupled with an increase in dosing frequency and primarily involves patients with a severe and/or a scarcely responsive disorder; more than once-daily dose, high symptom severity and resistance to antipsychotics have autonomous contributions to poor medication adherence. Furthermore, patients with unrecognised non-adherence are almost systematically exposed to high doses of antipsychotics, because they are erroneously classified as non-responders.

Irrespective of the nature of the link between antipsychotic dose and medication-taking behaviour, clinicians should systematically regulate their practice based on the fact that even small deviations from the prescribed drug regimen may have a strong risk for a psychotic exacerbation [85]. However, "whether the current clinical practice of prescribing the lowest amount of psychiatric medication to ameliorate

symptoms while keeping side effects at the minimum might be contributing to a situation in which there is very little allowance for even partial nonadherence" remains an unresolved issue that merits systematic monitoring.

Composite Contributors

Patient preferences, therapeutic alliance, and attitude towards medication come under the heading of composite determinants and moderators of adherence to antipsychotic medication.

Patient Preferences In recent years, the decisional process leading to the selection of therapy has progressively shifted from a model strictly directed by the doctor to a shared approach in which the patient's preferences and point of view have an appreciable role. This evolution has also been found to be important with regard to medication adherence. A recent experience [406] based on the use of psychiatric advice directives that "allow individuals with severe mental illness to document preferences for future treatment if they lose decisional capacity during a psychiatric crisis" is paradigmatic in this regard: "receiving at least one requested medication at the 12-month follow-up predicted greater adherence at 12 months", with an OR equal to 7.8.

The involvement of patient preferences on medication-taking behaviour is mediated by a set of direct and indirect effects. For example, the active participation of the patient is an essential constituent of therapeutic alliance and attitude towards medications, two well-established contributors to medication adherence. Furthermore, the active participation of the patient has a direct influence on the extent to which a patient's behaviour coincides with the prescription of the treating physician. Preference for a specific drug formulation is paradigmatic in this regard. Early evidence of a link between the formulation of a medicine and adherence can be traced back to the early stages of clinical psychopharmacology. For example, in 1967 a pioneering report [291] demonstrated how urine tested by the Forrest reagent changed from negative to positive in patients with schizophrenia who were switched from chlorpromazine in tablet form to an identical dosage of the liquid formulation. This initial finding has been partially confirmed in more recent years. Compared with standard tablets, the orodispersible tablets of olanzapine have been found, although not systematically, to be associated with improved medication adherence and/or efficacy [407–411]. However, the possible beneficial influence of the orodispersible tablets on medication-taking behaviour cannot be considered merely as a direct consequence of the preference attributed by patients to this specific formulation. The association has also been observed [410] in patients unaware of the specific formulation received because they were enrolled in a double-blind, double-dummy study. An alternative mechanism should therefore be hypothesised. Of particular interest is the emergence of a limiting weight gain effect mediated by sublingual absorption [410] because this might, in turn, facilitate medication adherence, at least in people prone to the weight gain phenomenon.

The influence of the drug formulation on medication adherence is not confined to comparisons between drops and tablets or orodispersible and conventional tablets; long-acting injectable antipsychotics are also of interest. The depots are likely to provide the best testimonials of an association between drug formulation and medication-taking behaviour, because they confer a reasonable benefit over oral agents on the global outcome [13, 68, 412–418]. There are two main advantages: long-acting antipsychotics offer a time-saving and money-saving solution to the problem of inveterate intentional refusal to take the prescribed therapies and make unintentional deviations from medical advice by the patient transparent. The pro-adherence effect of the depots can be reconciled with patient preference using this formulation. The literature suggests that, on the whole, individuals with schizophrenia accept long-acting injectable antipsychotics well, although studies are far from being univocal in their conclusions [408, 415, 419–423]. Reports in favour of depots over oral agents are contrasted by others that go in the opposite direction or fail to detect appreciable differences. These discrepancies are largely due to reporting bias, selection bias and other peculiar confounders. For example, in a sample of depot-naive patients with schizophrenia, only 23.4 % were reported to accept long-acting injectable antipsychotics, a rate definitely inferior to the 45.3 and 73.3 % observed in groups of individuals previously or currently treated with depots, respectively [408].

Therefore, there are good reasons for hypothesising that exposition to a defined formulation guides individual preference to an appreciable degree, with a stronger driving effect when the formulation, oral or depot, is taken contingently [408, 422]. This link is probably the expression of a generalised trend; it has also been documented in a comparison of orodispersible and conventional tablets of olanzapine [411].

The preference for an oral or a long-acting injectable antipsychotic also depends on the specific agent under review. The results of six studies included in a systematic review [419] are paradigmatic in this regard: five studies compared oral and long-acting first-generation antipsychotics and reported higher rates of preference for the depots, whereas the study in which the oral formulation emerged as the winner involved a comparison between risperidone tablets and long-acting conventional depots. Considering the differences that occur between atypical antipsychotics [14, 15] and the increasing number of second-generation depots available, the efficacy and safety profiles of each agent will have a greater influence on patient preference for a specific drug formulation in the near future.

A further moderator of individual preference for a specific drug formulation is the level of voluntarism that sustains patients in taking their medicines. The presence or perception of force or coercion is a common feature in patients exposed to antipsychotics in general [196, 231, 247, 286, 297, 424, 425]. In a group of outpatients with schizophrenia or schizoaffective disorder undergoing voluntary maintenance therapy, only 12.5 % denied any concern about coercion [425]; this seems enough to depict how common the phenomenon is. The observation that patients hospitalised “on an involuntary basis reported more decisions that they would have made differently than patients being treated voluntarily”

explains why these patients are extremely vulnerable to poor medication adherence [426]. The association between coercion and poor medication-taking behaviour is relative, as exemplified by the report [427] of a lack of differences in medication adherence among patients admitted voluntarily and involuntarily with a first episode of psychosis. The formulation of the drug has some specific relevance in relation to the level of forced medication. From this specific point of view, the disadvantage of depots seems intuitive considering that, unlike the oral formulations, they are "given rather than taken" [425]. Experimental evidence supports this statement indicating that, compared with individuals treated with an oral formulation, patients treated with long-acting injectable antipsychotics have higher scores related to perceived coercion and negative pressure [425]. This finding is not surprising. Many physicians restrict the use of long-acting injectable antipsychotics to patients who refuse or are reluctant to take medicines as prescribed and both patients and doctors frequently state that the depots are not appealing because they promote stigma. The observation [408] that two-thirds of patients who experienced a depot prescription as a compulsory measure quickly suspended the treatment demonstrates the unfavourable impact of lack of voluntarism in taking medicines. A report [392] that patients admitted voluntarily responded better to compliance therapy gives further indirect support to this conclusion. This evidence strengthens the need for ad hoc interventions to give patients a genuine role in the decisional process that leads to the choice of a long-acting injectable antipsychotic. To do this, however, we first have to change the culture of many psychiatrists, because they often have a negative or a non-positive attitude to the depots [428]. This explains why, assuming comparable rates of relapse after treatment with oral or depot antipsychotics, 81 % of doctors reported that they would recommend the oral formulation [429] Therefore, it is not surprising that, in a questionnaire completed by 246 psychiatrists attending the eighth World Congress of Biological Psychiatry, "less than 36 % of participants' patients have ever been offered antipsychotic depot treatment" [430]. Similarly, in a study in the canton of Zurich [420], 75 % of the psychiatrists interviewed reported that "they informed their patients about different formulations including the options of depot treatment", but 68 % of them also acknowledged "that patients are not sufficiently informed about different methods of administering antipsychotic drugs", a conclusion confirmed by the high proportion, 67 %, of patients who said that "they did not receive information about depot antipsychotics from their psychiatrist". This difference between the opinions of patients and doctors is especially discouraging from a clinical perspective considering that in a group of patients with schizophrenia who were uncertain about whether to continue the depot or not, 87 % decided to persist with therapy after a dedicated psychoeducational intervention [431]. Supplementary evidence of the propensity of the psychiatrists to overestimate their engagement in the search for active involvement of patients in the decision-making process comes from a German study that estimated the participation of patients at 70 and 83 % according to the judgement of patients and doctors, respectively [426]. Working on patient preferences may therefore be regarded as a fruitful strategy to improve adherence, provided this direct

intervention does not take the place of others aimed at consolidating therapeutic alliance and attitudes to medication. These three factors have certain relevant points in common. Nevertheless, they do not seem to be merely synonymous, because current drug formulations have been reported to be associated with medication preference but not to predict attitudes to antipsychotics [422].

Therapeutic Alliance Therapeutic alliance recognises two undisputed protagonists: the doctor and the patient. The doctor contributes professional competence, interest in medicine-based shared decisions, communicativeness and empathy. The patient participates with personal existential background in general, illness and treatment history and contingent expectations. However, the environment plays a supporting relevant role because it interferes with the efforts of the doctor and patient to build the alliance.

The relevance of the link between therapeutic alliance and adherence of patients with schizophrenia is far from being a recent discovery. Almost half a century ago [379], for example, it was reported that 39 % of outpatients treated by a physician "who viewed medications as less than essential" defaulted in medication regimens, whereas patients cured by a physician "who viewed medications as essential in the outpatient treatment of chronic schizophrenia" defaulted in therapies with a 25% rate. In successive years, the conclusion that a valid and trusting patient–doctor relationship promotes the perception among patients that there is a need for continuity of care with prescribed medications has been vigorously supported. Antipsychotic drugs are included in this general rule ([88, 111, 186, 196, 221, 231, 248, 288, 296, 303, 309, 432, 433]; for supplementary references, see [38, 47, 64, 98, 214]). A number of reinforcements directed to the patient may turn a valid therapeutic alliance into good medication adherence. These include optimism about the usefulness of the prescribed medicines, correct expectations about the risks and benefits of the therapy, interest in understanding the illness, meaningful involvement in the therapeutic project and realistic perception of the therapist, together with responsibility and self-control for the treatment. "The fact that patients usually show better compliance and better treatment response rates in clinical trials than in real-life settings" [434] may be viewed as a demonstration of the relevance of this long list of factors on individual medication-taking behaviour.

Irrespective of the underlying moderators involved, the impact of therapeutic alliance on medication adherence is relevant. For example, a longitudinal study [88] has shown that every one-point increase in WAI score was accompanied by approximately a 5 % reduction in the risk of becoming non-adherent. The fact that patients with schizophrenia included lack of trust in the provider (i.e. a proxy for poor therapeutic alliance) in a list of the top ten barriers to medication adherence [230] may be considered a further indication that a valid alliance is a relevant prerequisite for taking medicines as indicated by the prescriber. Therapeutic alliance also has an indirect role on medication-taking behaviour. The ability of the doctor to work with the patient is crucial for linking individuals discharged from hospital to outpatient specialty facilities deputed to ensure long-term

assistance and medication adherence. In this regard, the report [435] that 65 % of patients failed to attend scheduled or rescheduled initial outpatient appointments is a dramatic warning, even though the need for continuity of care has recently been emphasised. In a comprehensive review [47] that assessed numerous risk factors for poor adherence in people with schizophrenia, inadequate hospital discharge planning was included in the list of the variables most consistently associated with patient deviation from medical prescriptions.

Attitude to Medication The composite origin of attitude to medication is well supported. A study in which structural equation modelling was applied to a wide number of variables concerning 228 patients admitted consecutively with a diagnosis of schizophrenia or schizoaffective disorder [221] illustrates this. Attitude to medication was found to be "predicted by insight, relationship with staff (especially the physician-prescriber), and the patient's admission experience" [221], whereas a poor relationship with the prescriber, experience of coercion during admission and low insight were the main predictors of a negative attitude [221]. The same study also reported that attitude to drugs was more marginally influenced by medication knowledge and symptoms but substantially untouched by adverse events. The assessment of adverse events using the LUNSERS could have influenced the observation that iatrogenic health effects failed to have appreciable effects on adherence; the scale examines the objective presence of an adverse event rather than the severity of the associated subjective distress. Furthermore, as an expression of subjective interpretation of changes related to the pharmacologic therapy [436], attitude to medication includes other contributing factors such as symptom severity, functioning, personality traits, previous experience with antipsychotics, societal and familial attitude to psychoses and their treatment and possibility of access to health care services.

The issue of a link between medication adherence and attitude to antipsychotics is far from new. For example, in a 1964 report [247] on attitude to drugs of 30 inpatients with schizophrenia known to be acceptors or refusers of neuroleptics, the group of extreme refusers rated medicines less favourably. The negative influence played by low attitude to medication on adherence has been substantially confirmed over the years, although with some discrepant findings ([92, 113, 181, 185, 197, 221, 231, 240, 241, 246, 247, 249, 289, 294, 299, 303, 319, 320, 325, 327, 374, 388, 391, 436–439]; for supplementary references, see [38, 47, 64, 98, 214]). The reported association [324] between attitude to treatment and efficacy of compliance therapy indirectly corroborates this trend.

What remains is a largely unanswered issue: whether the driving role played by a negative attitude to antipsychotics on poor medication-taking behaviour involves not only actual but also hypothesised attitudes. One study [391] that explicitly tested the influence of hypothesised attitudes using the willingness of the patients to give the same "antipsychotic to their children, if they would have the same illness" suggests this last possibility could be realistic.

Predictors

The many heavy burdens imposed by poor adherence to antipsychotics and the existence of interventions that can successfully combat it justify the claim that individuals at risk for non-adherence must be identified promptly. Evidence of unexpected negative outcomes could constitute a first useful warning sign but this is a very rough index and has an appreciable risk for false positives. More powerful determinants and moderators of medication-taking behaviour would be more appropriate. However, extensive application of this approach may be restricted by the need for data collection requiring competences exceeding those typical of the daily clinical routine. Valid and easily accessible markers devoid of any causal influence on medication adherence may be a useful tactic to surmount many of these limitations.

Age and ethnicity of the patient, together with previous medication adherence are included among non-causal markers useful for identifying patients according to medication adherence.

Age The influence of the age of the patient on adherence to antipsychotics has been tested with mixed results ([51, 59, 61, 79–81, 91, 113, 147, 159, 187, 196, 197, 210, 234, 241, 258, 285, 287, 291, 294, 298, 320, 324, 325, 334, 337, 385, 440]; for supplementary references, see [38, 47, 64]). Overall, when present, the association with age has almost systematically supported the conclusion that younger patients are at an increased risk for poor adherence. The result is not completely surprising. In agreement with the Health Belief Model [98], younger patients are "less likely to appreciate the severity of their illness or the need for medication" [80] because they lack direct personal experience with schizophrenia and its treatment, and generally have few opportunities to interact with a chronic patient who may act as a testimonial. Common evidence that people with a first-episode schizophrenia are particularly sensitive to metabolic and extrapyramidal adverse events [6] supports the hypothesis that iatrogenic health effects contribute to the development of the association between young age and poor medication adherence.

The observation, derived from the Calgary Early Psychosis Programme [91], that, among patients with first-episode schizophrenia, those presenting poor adherence were relatively younger suggests that the Health Belief Model is probably not enough to fully explain why younger individuals fail more frequently to follow medical advice.

Whatever the causal mechanisms involved, the fact that younger patients have more difficulties in taking prescribed medicines may be used successfully in clinical routine to identify first-choice candidates for interventions to monitor and promote good medication adherence. This is further justified when one considers that younger patients with problems of adherence have been reported to correct this specific behaviour quickly [88].

The presence of a preferential link between young age and poor medication status implies that the probability of being adherent may increase with age. This progression plausibly occurs until full adulthood but does not apply to the elderly. A long list of elements have led to the hypothesis that a second peak of increased risk for poor medication-taking behaviour occurs in old age. For example, elderly patients with schizophrenia inevitably incur age-related pharmacokinetic and pharmacodynamic changes [441]. Furthermore, elderly patients are more subject to cognitive and memory deficits, frequently receive insufficient social support, are more likely to be incapacitated in physical dexterity due to disparate medical comorbidities, and present an increased risk of perceiving medicines as unnecessary [202]. All these factors contribute to poor adherence as a result of unintentional oversight in taking medicines, more complex polypharmacotherapies and sensitivity to the unwanted effects of medications. This relevant theoretic framework, however, has not been accompanied by sufficient experimental support so far. More precise information on this issue is necessary. Two supplementary considerations are important: the increase in life expectancy over the last century [442] that has multiplied many-fold the number of people aged 65 years and older; the common observation that, in clinical practice, many elderly patients with schizophrenia or paraphrenia are treated with low doses of antipsychotics [443], with the consequence that they may be extremely vulnerable to even marginal deviations from the prescribed regimen.

Ethnicity Some effect of ethnicity on medication-taking behaviour has been frequently but not systematically reported in the literature ([51, 61, 80, 81, 89, 111, 137, 147, 159, 187, 207, 210, 241, 258, 285, 298, 334, 367]; for supplementary references, see [47, 64]). The link has emerged more commonly in US studies involving multi-ethnic samples of patients with schizophrenia. In general, African Americans, Mexican–Americans, Latinos, Chinese and Asians have been found to be at higher risk for poor adherence to antipsychotics than non-Latino whites.

Despite the many positive findings reported, the conclusion that ethnicity represents "an imperfect flag for other factors that underlie adherence" [80] seems to be absolutely right. In the link between medication-taking behaviour and ethnicity, second-order associations play a major role. Unfortunately, the list of second-order associations that could mediate the apparent effect of ethnicity is substantial. Susceptibility to adverse events, culture, acculturation, language proficiency, level of familial and social support, income, trust in alternative medicine, religion, integration, immigration status, racial tolerance of the leading community, rights of minorities, inequalities in the standard of care, barriers to a valid patient–doctor and patient–provider relationship and opportunities to fully benefit from educational campaigns on schizophrenia and its treatment are some of the most obvious headings. In addition, patient–doctor interethnic and intercultural differences may make establishment of a valid rapport more difficult and facilitate the risk of a misdiagnosis [444]. In both cases, the probability of poor medication

adherence increases as a result of an invalid therapeutic alliance and prolonged exposition to the unpleasant effects of therapies devoid of appreciable clinical benefits. Furthermore, under-prescription of second-generation antipsychotic may be mediated by ethnicity. For example, in a sample of 36,575 community-dwelling Medicaid beneficiaries affected by a severe mental illness, the "odds (of Blacks) of receiving a newer atypical antipsychotic were less than half of White and Other minority beneficiaries" [440]. This scenario is even more complex, because the representativeness of individual ethnic groups and opportunities for integration are susceptible to relevant variations over time and between countries. The effect of ethnicity on medication-taking behaviour, however, does not seem confined to sociocultural factors. Ethnic stratification was reported to exert a pharmaco-specific moderating effect not only on the risk for metabolic syndrome [390] but also on the association between treatment response and defined genetic variants [445].

Given this complexity, it is easy to understand that achieving valid and generalizable conclusions about the role of the different contributors grouped under the ethnicity label is at least problematic. Third-order associations are also likely to operate. For example, in a large-scale study that tested adherence to antipsychotics among non-Latin whites, Latinos and Asians with schizophrenia and considered the English proficiency of the two minority groups, "Latinos with limited English proficiency were more likely than English-proficient Latinos to be medication adherent and less likely to be excess fillers", whereas "Asians with limited English proficiency were less likely than English-proficient Asians to be adherent, more likely to be nonadherent, and less likely to be excess fillers" [187].

Regardless of the underlying mechanisms involved, the evidence is that associations with medication adherence that are valid for one ethnic group may not be completely applicable to another, and this variability is a relevant complication for psychiatric services that care for ethnically and linguistically diverse adults with schizophrenia.

Previous Medication Adherence Previous adherence to antipsychotics is not a favourite topic among studies examining predictors of medication-taking behaviour. Nevertheless, when tested, this variable has systematically been shown to have a valuable predictive power ([19, 51, 80, 88, 93, 111, 127, 241, 245, 301, 323, 388, 446]; for supplementary references, see [38, 47, 214]).

Findings from 1,579 patients with schizophrenia treated with any oral antipsychotic who were enrolled in the US-SCAP study are particularly informative [51]. This prospective observational study focused on "39 previously reported potential risk factors of nonadherence with antipsychotic medication" related to the patient, the environment and the treatment demonstrated that the single best predictor of future adherence was patients' previous adherence (OR 4.14) and 78.5 % of subjects were accurately classified. The accuracy level was driven primarily by a high positive predictive value (86.6 %) and a moderate negative predictive value (43.9 %).

Overall, that a personal history of previous adherence to antipsychotics is a predictor of future adherence is understandable. Although transition from adherence to non-adherence is not an exceptional event and the opposite may occur, especially when dedicated interventions are predisposed, antipsychotic-taking behaviour may be regarded as a relatively persistent phenomenon.

With regard to the principal mechanisms sustaining the predictive value of previous medication-taking behaviour, it seems reasonable to argue that factual experiences with psychopharmacotherapies rather than pre-existing attitudes exert a preferential involvement. In a small, clinically heterogeneous group of never-treated patients with a first episode of psychosis, the initial personal prediction of compliance has been shown to have low reliability based on compliance observed over 3 months [294]. Furthermore, the demonstration that "past antipsychotic use rather than receipt of a specific medication was most associated with future antipsychotic adherence" suggests that "what patients know and do as a result of prior medication or illnesses experience … is a more robust predictor of future adherence than the receipt of a specific medication" [378].

Present and Medium-Term Perspectives

In 1992, a review on medication adherence in general [447] concluded that "more than 20 years of research in the area of compliance has produced very little consistent information on the factors which can be correlated with non-compliant behaviour". Twenty years of intensive, worldwide, dedicated research have elapsed since then and we have certainly learned a lot about the dimension, the consequences and the contributors of poor adherence to antipsychotics in people with schizophrenia. Nevertheless, much more remains to be learned. Furthermore, relevant limits continue to affect these studies and this level of evidence explains well why the phenomenon of medication-taking behaviour continues to be "far better documented than understood" [64]. Therefore, urgent requirements have emerged not only for a critical analysis of the evidence accumulated so far but also for the planning of new research.

One lesson that has been learned refers to the persistent validity of the old sentence that "the answer to the question 'is this patient taking his drug?' will depend on the criterion used" [30]. The innumerable measures of medication adherence used so far have generated results that are only partially comparable. Furthermore, and this is even more relevant, no measure is faultless. Therefore, the ideal gold standard of reference is not at our disposal and the perfect measure that may be easily, systematically, and cheaply used probably does not exist.

On the other hand, a doctor's ability to identify patients presenting poor adherence to antipsychotics is certainly better than indicated by the sentence, referring almost half a century ago to the intake of antacids, that "the physician ability to distinguish those patients who adhered well from those who adhered relatively poorly was no better than might be expected by chance" [69].

Nevertheless, when they have to identify which clients fail to follow their prescriptions, the clinicians of today continue, in the absence of dedicated interventions, to have difficulties so that even the worst measure would be more reliable than the personal feeling of the doctor [69]. Consequently, we are forced to use at best the imperfect measures of adherence currently at our disposal, searching in the meantime for consensus guidelines to make the results of independent experiences comparable.

While waiting for consensus, it may be useful to follow, for example, the proposal to always report "an estimate of the mean percentage of medication taken as prescribed during the follow-up period" and "include at least two measures of adherence" [37]. This approach, however, may become burdensome not only for practical purposes but also for research.

Clinicians and researchers should also keep in mind that measures that are strongly indicated for research may be less indicated for clinical practice and vice versa. In research on medication adherence, for example, it is essential that the adopted measure does not require the active voluntary cooperation of the patient. In the absence of this requirement, it is likely that individuals who are reluctant to strictly follow the advice of the physician will refuse to participate or deliberately develop surreptitious deviations from usual adherence. These two decisions imply that the products of the research, that is the results, cannot be generalised. Within this scenario, refilling of prescriptions reported in pharmacy databases seems to be one of the best options, at least in countries that guarantee universal drug coverage or adopt other close pharmacy systems. Despite the presence of some weaknesses, this approach has advantages over other indirect measures because it does not imply any active voluntary cooperation of the patient, the costs are reasonable, it is not time consuming, permits collection of data from numerically representative populations, and may be used in longitudinal studies aimed at evaluating eventual changes in treatment adherence. Measures indicated for clinical practice must also satisfy some of the prerequisites that are especially useful in research, such as convenience, low cost, not time consuming and can reveal eventual modifications of medication-taking behaviour. However, measures for clinical practice do not require the exclusion of active participation of the patient. In this specific setting, active participation could even be recognised as an added value because in the daily routine, the treating physician is also engaged with the need to reduce poor adherence and reinforce good adherence. For these purposes, active involvement of the patient has a positive influence due to a continuous sensibilising effect. A recent proposal [448] to use a cellular phone with a camera to photograph medicines in the patient's palm just before taking them, which would time stamp when the photo was taken, is a new and promising strategy. Although photos do not ultimately prove that the patient ingested the therapy, this method, like MEMS, can document adherence to prescription timing and perform repeated evaluations and has the appreciable advantage that it is cost-effective, easy to use and based on widely available equipment.

Another lesson extrapolated from an overview of the current literature is that clinicians should desist from consuming too much of their time in debates about the precise percentage of people with schizophrenia who are poorly adherent to antipsychotics. Low concordance rates between independent measures and the diffuse risk of multiple selection biases address this issue coherently. Furthermore, it is already known that the proportion of individuals who do not take antipsychotics as prescribed is large enough to merit systematic study.

The promotion of head-to-head studies that use the same measures to test for adherence typical of distinct clinical conditions should be strongly encouraged, because this substantially neglected approach is relevant in order to reach valid conclusions about the trans-diagnostic rather than disease-specific or mixed nature of the processes underlying medication-taking behaviour.

In addition, the consequences of poor adherence to antipsychotics have been extensively explored over the years in almost all its principal aspects. Unrecognised poor adherence and costs, especially indirect costs, imputable to a failure of patients to follow medical advice correctly are the main partial exceptions. Because more precise knowledge on these two issues is relevant to understand the global impact of poor adherence, studies on these specific topics would be welcome.

Another area that calls for renewed experimental interest comes from the old observation that "trials based on unsupervised oral medication have probably been built on very unsure foundations" [449]. As emphasised earlier, clinical trials commonly use a rough measure of adherence, the simple countability of returned pills, despite the fact that failure to take medications meticulously adds variance to the results and thus weakens the statistical power. This fragile approach needs to be reversed. Stratification of the results according to adherence levels is a prerequisite for reaching more definite answers to some issues that are essential for regulatory purposes, in particular the superiority of a new drug compared with marketed comparators, the precise identification of therapeutic dose ranges and the anticipation of first-line candidates for special monitoring in post-marketing pharmacosurveillance [450, 451].

A point that probably does not merit any further motivation pertains to the search for new determinants and modulators of medication adherence. The issue has been extensively tested in a large number of studies and the list of proven contributors is ample enough to justify the assumption that absolute omissions seem unlikely or, if present, are candidates to explain only a marginal quota of variance. This does not mean that current knowledge on single factors involved in the adherence process is exhaustive. Premorbid functioning, personality traits, temperament and genetics are sufficiently representative of this. However, the central contribution that the subjective feelings of the patients play on medication-taking behaviour requires closer reassessment. The progressive shift from compliance to adherence as the preferred label, the common referral to the Health Belief Model, the pressing emphasis in favour of shared decisions, and, more broadly, the claims that the preferences of the consumers are valued, coherently address the issue. Nevertheless, studies on contributors to medication adherence

continue to be anchored to a medically centred approach that leaves the opinions and expectations of the patients at the periphery to the point that they may be interpreted as repressive, as if the failure to follow the advice of the doctor merits blame. Excluding any blaming intent, this approach is wrong because it minimizes a priori the possibility of improving adherence based on patient preferences, shared decisions and therapeutic alliance. A strong call for taking the point of view of the patients seriously comes from the demonstration that doctors and patients frequently conceive adherence and the various pros and cons of the therapy in a conflicting way, to the point that what is important for one may be irrelevant for another [397, 452–456]. For example, the indication posited by patients of a clear hierarchy of preferences in which "the strongest priorities were placed on reducing confusion and increasing energy" [455] is in sharp contrast to the scarce attention that doctors generally pay to these two items. The impact of this and similar mismatches may be overwhelming for both research and clinical practice.

In the future, even with full knowledge of all the contributors to medication adherence, attempts to transfer into clinical daily routine an easily accessible, ready to use identikit of those patients with schizophrenia who are especially predisposed to poor antipsychotic-taking behaviour seem doomed. A number of considerations lead to this pessimistic conclusion. First, the number of susceptibility and plasticity factors that govern medication-taking behaviour implies very small to small levels of variance explained by each single contributor. Furthermore, the coexistence of protective and vulnerability factors, the presence of complex interplays between independent, addictive and interactive effects, relevant participation of indirect associations and variable expression of individual contributors among people with schizophrenia strongly limit the possibility of classifying individuals with poor or good adherence. Therefore, clinicians may at best target only some more or less reliable indicators of adherence. Previous medication-taking behaviour, eventual comorbidities with substances use disorder, young age, a history of repeated rehospitalisations and belonging to a minority are the most valuable factors. Although these accessible variables are imperfect indicators of adherence, they are better than nothing, because they may help clinicians in their efforts to direct the resources at their disposal to identify and manage medication adherence. Restriction of social and health care funds worldwide add value to this approach.

The statistical support necessary for better knowledge of poor adherence to antipsychotic plausibly requires innovation. Multivariate statistical models have so far provided essential support in improving global understanding of the mechanisms that sustain adherence to antipsychotics. Nevertheless, classic multifactorial statistics on group effects are only partially useful to predict individual proneness to poor medication-taking behaviour and identify the first-choice interventions for improvement. To this aim, statistical procedures centred on the single patient, for example artificial neural network analysis, are a useful approach. Unfortunately, these models have rarely been applied to the medication adherence phenomenon so far.

A number of appreciable unmet needs therefore persist in the field of research on medication-taking behaviour of people with schizophrenia. However, the most pressing demand involves what we can expect from systematic application of interventions in the daily routine aimed at improving adherence to antipsychotics. This question is not trivial. The prognosis of schizophrenia continues to be unfavourable in a significant proportion of patients despite the definite progress since the advent of second-generation antipsychotics. The search for new and better antipsychotics must therefore be pursued. Nevertheless, the observation that, compared with agents already in the market, "a hypothetical new medication that is 50 % more efficacious would decrease 1-year postdischarge rehospitalisation rates by 18 %" [122] does not leave room for excessive optimism, because agents with such clinical potential are not just around the corner. Thus, there are good reasons for strong investment on strategies to improve medication adherence; the hope for better standards of care granted by the antipsychotics of the future will remain a largely empty promise in the absence of adequate control of medication-taking behaviour. This conclusion is in agreement with the estimate that "improving compliance by 50 % would decrease 1-year rehospitalisation rates by 12 %" [122], i.e. a rate close to the estimate for drugs of the future, which are outside our current expectations. Fortunately, many of the contributors to poor medication adherence are modifiable as a result of several intervention. Some do not require expertise outside the standard professional education. Others need the involvement of ad hoc trained personnel.

Interventions that are within the reach of any mental health team include communication respectful of the patient, information adequate for formulation of valid consent and at low risk of error by patients, preferential use of drugs at the lowest efficacious dose, judicious reduction of polypharmacotherapies to the minimum required and systematic revision of prescriptions, so that therapies that are no longer necessary are ceased. Although all these pro-adherence strategies must be planned throughout the process of care, they should be intensified concomitant with discharge from hospital or, more broadly, during recovery from an acute episode of psychosis. As emphasised earlier, this period is at special risk for the emergence of poor medication adherence and incomprehension in the doctor–patient communication. Therefore, the proposal [457] of a "transition coach" who governs the passage from hospital to community care could be rewarding and cost-saving for psychiatric patients.

Another easy and direct strategy that may lead to improved medication adherence in patients who are strongly reluctant to follow the prescriptions of the treating physician involves a more systematic use of the long-acting injectable antipsychotics [416]. The use of this specific formulation in clinical routine is limited in many countries due to persistence of several barriers, in particular, the reluctance of doctors to prescribe long-acting antipsychotics, the scarce information for patients and families about these agents and the patients' perception of being under unusual coercion by the treating physician. The time is now right for a turnaround. The recent commercialisation of different long-acting second-generation antipsychotics and the approach of others to the market provide an excellent

opportunity for removal of these barriers because individualised use of the depots is now possible.

In recent years, an increasing number of non-pharmacologic interventions that require special training have also gained ground to combat the susceptibility of people with schizophrenia to poor adherence to antipsychotics [458, 459]. Despite the vast literature, the cost effectiveness of the different approaches, the identification of obstacles to their extensive use in clinical routine and the selection of the eventual front runners among the various interventions await more definitive answers. To this aim, supplementary head-to-head comparisons are particularly indicated.

Stigma against severe mental disorders and psychopharmacotherapies is among the areas of intervention that merit priority funds. Despite the message that schizophrenia has solid biological origins, and thus is to be viewed as a disorder like any other, and is a leading factor in the widespread war on stigma, large sectors of society continue to have stigmatising attitudes. Therefore, the anti-stigma campaigns of the future need to be radically changed to provide alternative messages with major emotional resonance. However, current straitened circumstances force us to identify target priority groups for anti-stigma interventions given that improvements in this area imply discrete time latencies before their beneficial effects may become tangible. High school students are a good first-choice population. Young people are especially receptive to anti-stigma messages, because they have been reported [226, 228] to be at a minor distance from people with schizophrenia. Furthermore, with successful intervention, students disseminate their position against stigma for many years, thus diluting the prejudices of the lay public further in the long term. Teachers, professional figures operating within the health care system, politicians and people close to patients with schizophrenia are also reasonable figures of elective reference. Due to their pedagogical expertise, teachers are central to students' education and may become autonomous promoters of supplementary anti-stigma groups. The importance of professional figures within the health care system resides in the fact that they are in charge of reinforcing the message that antipsychotics are mandatory in the therapy of schizophrenia. In addition, the anti-stigma commitment of politicians is essential because they control the funds necessary for anti-stigma campaigns. The people close to patients need dedicated interventions because they too may experience stigma, sometime stigmatize the affected member of the group, and are always in the forefront for abating poor medication adherence.

An ultimate need that is persistently unmet is the inability to convert the many pro-adherence interventions into an opportunity for truly individualised countermeasures. This relevant advancement presupposes systematic access to statistical support that can define the weight of the various contributors of medication-taking behaviour in each individual patient and to insert these estimates into a model that takes into account the margin of improvement granted by the different interventions for any specific area. None of these conditions are even vaguely applied in current clinical practice.

Closing Remarks

Accumulated evidence promises new possibilities for the recognition and management of poor adherence to antipsychotics in people with schizophrenia. Nevertheless, unless the gap between what we know about the issue and what we use in our clinical work is drastically reduced, this progress risks remaining largely a dead issue. Consequently, the old maxim "every patient is a potential defaulter. Compliance can never be assumed" [401] will continue to express a nihilistic message that it is impossible to discriminate good and poor medication-taking behaviour rather than a simple, descriptive message that non-adherence may be always imminent.

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Pharmacological Strategies to Enhance Adherence in Schizophrenia

Alex Hofer and Wolfgang Fleischhacker

Introduction

Schizophrenia is a serious and disabling mental illness that substantially impacts upon a patient's capacity to achieve or maintain employment and relationships. In addition, schizophrenia has a huge societal effect, posing a challenge for families, caregivers, and healthcare systems.

Generally, early detection and intervention are associated with a better course of schizophrenia and an improved outcome. Most current guidelines recommend continued antipsychotic medication for 1–2-years following a first episode of schizophrenia [1–4]. During this period antipsychotic discontinuation is strongly associated with relapse [5], however, a minority of patients might not need medication to prevent relapse [5, 6]. On the other hand, withdrawing antipsychotic treatment according to the above-mentioned guidelines has been associated with a relapse rate of almost 80 % after 1 year post discontinuation and 96 % after 2 years [7]. Similarly, intermittent treatment, i.e., tapering medication once a patient is in remission and restarting it when early warning signs emerge, is less efficacious than continuous treatment, both in first-episode [8] and multiple-episode patients (e.g., [9]).

Hence, the effectiveness of antipsychotic drugs in reducing the risk of relapse is undisputed. In this context, a systematic review and meta-analysis of randomized, placebo-controlled trials revealed a significantly lower relapse rate during treatment with new-generation antipsychotics versus placebo [10].

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Importantly, even a very short treatment interruption can increase the proportion of hospitalized patients. For example, Weiden and coworkers followed patients for 1 year and found that the risk of hospitalization doubled following a gap in medication therapy of 1–10 days, nearly tripled if medication was not used for up to 30 days, and quadrupled following a gap of more than 1 month [11].

Altogether, only about 50 % of schizophrenia patients can be expected to be fully adherent to treatment with medication, i.e., to take 80 % or more of the prescribed medication. The remaining patients are either partially adherent, taking 50 % or more of medication and either reducing the dose or failing to take medication from time to time, or may not follow prescription instructions at all [12, 13].

The degree of adherence is generally overestimated by psychiatrists, patients, and their relatives (e.g., [14, 15]). In addition, the attitude of professional careers toward the illness and the treatment plan are factors, which may influence patients' attitudes toward the illness and medication and consequently adherence. For example, Rettenbacher and coworkers reported that only 35 % of nonmedical professionals, 46 % of psychiatric nurses, and 29 % of psychiatrists would be willing to take antipsychotic medication, if hypothetically suffering from schizophrenia. It is clearly extremely difficult, if not impossible, for staff to motivate patients to adhere to treatment recommendations, if they are not convinced about the need for medication themselves [16].

The majority of patients have adherence problems at some point [17]. A recent review of the literature reported rates of 15–40 % during the first month of treatment, and 50 % by treatment month 6 [18]. This proportion increases up to 75 % within 2 years [19]. Importantly, adherence rates are equally problematic for antipsychotic *and* nonpsychiatric medications [20, 21].

The clinical consequences of nonadherence to pharmacological treatment include an increased risk of relapse, rehospitalization, and antipsychotic treatment resistance [22, 23]. Further, nonadherence and partial adherence are associated with substance use, violence, arrests [24], suicide attempts [25], and poorer long-term functioning [24].

Pharmacological Factors Contributing to Nonadherence

Clearly, patients' reasons to adhere to a prescribed medication regimen and to remain on treatment are complex and variable. Interestingly, achieving symptom relief has been associated with poor adherence in first-episode patients, probably due to impaired insight into the need of maintenance treatment to prevent relapse [26]. On the other hand, as might be expected, nonadherence is more common when the patient perceives the benefits of medication to be suboptimal. In this context, it has been suggested that good adherence may lead to better response, which in turn leads to better adherence, while poor adherence may lead to poor response, which may further decrease adherence and increase the likelihood of treatment discontinuation [26].

In general, monotherapy results in better patient adherence than polypharmacy. Dosage regimen represents another pharmacological factor that may impact on adherence. Especially in elderly people neurocognitive impairment, which is commonly associated with schizophrenia, may represent a barrier to adhering to a complicated oral antipsychotic regimen [27]. A systematic review of the association between drug delivery systems and adherence to psychopharmacological treatment concluded that next to switching to oral slow-release formulations and depot injections a reduction in the frequency of administration, ideally a once-daily regimen, may improve adherence [28]. Similarly, Claxton et al. have shown that adherence of both mental health and nonmental health patients deteriorated with higher daily dosing frequency [29]. Interestingly, it has been reported that physicians are more likely to change or add medications in patients who are not fully adherent [30]. However, Bordenave-Gabriel et al. did not find an association between daily dose frequency and adherence [31], and in a recent European multicenter study a high daily dose frequency was associated with even better adherence [32]. Accordingly, patient preference for a specific regimen (even for more frequent dosing) may exert the dominating influence on adherence [33]. Furthermore, the route of treatment administration is discussed as having an influence on adherence. For example, positive attitudes toward liquid formulations or orally disintegrating tablets have been reported to indirectly facilitate adherence [34, 35]. The role of long-acting injectable antipsychotics is discussed in Psychological Issues in Improving Adherence and Alliance.

Safety, Tolerability, and Attitudes Toward Treatment

The link between antipsychotic-induced side effects and nonadherence is still an area of controversy. In both first-episode [36, 37] and multiple-episode patients [38] attitudes to drug treatment have been shown to be strong predictors of medication adherence. Naturally, side effects can induce long-term distress and functional impairment and thereby contribute to poor attitudes toward treatment. It has to be considered, however, that the subjective tolerability of antipsychotics varies considerably from one patient to another [38] and that it may not be the presence of side effects but the subjective relevance that patients give to these side effects that impacts on adherence [32, 39]. For example, extrapyramidal symptoms (EPS—mainly akathisia and akinesia), which have been reported to be of particular relevance in this context [40, 41], were not related to drug attitude in a US sample [42], whereas dyskinesia was associated with poor attitude in a Nigerian sample [43], but correlated with less negative feelings toward antipsychotics in Austrian patients [44]. However, these are data from cross-sectional studies and clearly attitudes toward medication may not only differ between individuals but also vary over time [17]. Prospective, naturalistic data from the European Schizophrenia Outpatient Health Outcomes (SOHO) study [45] indicate that there may be a negative correlation between changes in EPS and adherence [46]. Another investigation has not found such an association but emphasizes that

changes for the better in diminished sexual desire between baseline and month three of treatment might lead to a more favorable attitude toward drug treatment [47]. In line with this, cross-sectional studies have confirmed that both quality of life and adherence are affected by sexual dysfunctions [48, 49]. Furthermore, weight gain [50, 51] and sedation [43, 44, 52] can significantly impair patient adherence and functional outcomes.

While slowing of thinking, inner restlessness, or lack of psychic energy led to negative attitudes and impaired adherence in studies by Lambert et al. [48] and Awad [53], Rettenbacher et al. [54] found a positive correlation between the psychological side effects of antipsychotic medication (including concentration disturbances, loss of energy, etc.) and adherence and pointed out that it is often difficult to differentiate between these phenomena and negative symptoms.

Finally, it has to be emphasized that the therapeutic alliance between healthcare professionals and patients has consistently been shown to play a key role in patients' attitudes toward treatment and cooperativeness of taking medication as prescribed [55–57]. A sound relationship between a patient and a physician should therefore be regarded as a prerequisite to secure treatment strategies that allow maximum efficacy and minimal side effects, and, ultimately, adherence to medication. Accordingly, even if the target symptoms are treated optimally, a switch of medication should be considered in the case of tolerability problems.

If EPS emerge during treatment with antipsychotics, lowering the dose or adding an anticholinergic are usually the first interventions. Switching antipsychotics is a third option, especially in the case of EPS induced by first-generation compounds. Notably, switching to a new-generation antipsychotic can have a dual effect: novel antipsychotics have a considerably lower propensity to lead to EPS and the use of anticholinergics, which have side effects of their own, will most likely become unnecessary.

Spontaneous remission of sexual dysfunctions may occasionally occur [58]. Generally, before switching to a different drug that is less likely to cause the specific sexual problem experienced the dose of the prescribed antipsychotic should be decreased.

If weight gain occurs, dietary advice as well as advice on regular exercises should be offered before changing medication because of this side effect. Switching to aripiprazole (e.g., [59]) or ziprasidone (e.g., [60]) can reverse weight gain, but switching medication can lead to relapse and treatment discontinuation [59]. Pharmacological interventions (e.g., metformin [61]) are indicated when behavioral methods or switching have failed.

First- Versus New-Generation Antipsychotics

Compared to first-generation antipsychotics (FGA) new-generation agents (NGA) have less liability to cause EPS. It was hoped, therefore, that the increased use of NGAs would improve treatment adherence. Actually, some clinical trials have

found a modest advantage for NGAs in this regard [62–66], however, a large number of studies failed to show such a difference [32, 67–73]. A recent study, for example, investigated the relationship between medication-related factors and adherence in schizophrenia outpatients in four European countries and found the attitudes toward antipsychotic medication to predict adherence, whereas the type and formulation of drugs as well as side effects were not meaningful in this context [32]. Hence, regular examinations of patients' attitudes toward treatment and regular risk/benefit assessments may be of more relevance for medication adherence than the type of treatment.

Long-Acting Injectable Antipsychotics

Long-acting injectable (LAI) or depot antipsychotics are associated with a number of advantages as compared to oral compounds: when steady-state levels are achieved, a more controlled and constant input rate together with the circumvention of first-pass metabolism [74] is associated with a lower variability in the range of plasma concentrations [75], which in turn has been claimed to lower the risk of side effects (e.g., [76]). In addition, treatment with LAIs has been associated with early detection of relapse, improved relapse prevention, and reduced rehospitalization rates ([77–81], but see also [82]). Lastly, LAIs facilitate the differentiation between a lack of efficacy and poor adherence, which has important implications for subsequent treatment planning regarding the potential need to change the dosage or the medication. Furthermore, nonadherence is immediately obvious when the patient does not show up for the scheduled injection, thereby facilitating the opportunity for appropriate, early interventions including psychosocial treatment, which may result in improved long-term symptom control [22, 83]. However, treatment with LAIs clearly does not guarantee medication adherence. Weiden and coworkers, for example, found higher adherence rates in patients converted to LAI treatment during inpatient stay as compared to those who remained on oral medication at one month postdischarge, but no between-group differences in this regard at 6 and 12 months postdischarge [84]. Accordingly, factors such as medication beliefs and lack of insight can also reduce adherence to LAI therapies [85]. Nevertheless, in a number of studies treatment retention was significantly higher with injectable versus oral formulations (e.g., [78, 86, 87]).

Overall, it is important to see LAIs as a positive individual choice and not as a coercive method to solve difficulties with adherence.

Despite these advantages it is estimated that merely between one quarter and one third of people with schizophrenia are prescribed an LAI antipsychotic in the UK, a country in which LAIs are used more commonly than in many other countries [88]. On the part of the patients this might be due to fear that injections constrain their autonomy, are painful [89], or stigmatizing [90]. When asked to state a treatment preference (oral versus LAI), patients tend to favor their current

formulation [91, 92]. Many clinicians, on the other hand, are hesitant to use LAIs despite regarding them to be associated with better adherence ([93, 94] but see also [95, 96]) and assume, that they are not useful in patients sufficiently adherent with oral medication, that they are associated with more side effects, that patients always prefer oral medication, and that they should not be used in first-episode patients [93, 97–99]. However, recent studies suggest that the use of LAI medication is feasible in first-episode psychosis. Emsley et al. for example, conducted a 2-year study and reported on symptomatic remission in 64 % of first-episode patients who were treated with LAI risperidone with 97 % maintaining this status until study completion. Notably, patients in remission received lower doses of antipsychotic medication, had fewer EPS, and a more favorable attitude toward medication [100]. Importantly, almost all patients, who chose to discontinue medication after the completion of the study eventually relapsed [101]. In a prospective study by Weiden et al. first-episode patients were randomly assigned to a recommendation of changing to LAI risperidone versus continuing on oral antipsychotic medication following clinical response to oral treatment. At 12 weeks, patients accepting LAI treatment (73 %) were significantly more likely to be adherent than patients staying on oral medication [102]. Moreover, in a naturalistic study partial or nonadherence occurred significantly more often in first-episode patients who were treated with oral risperidone as compared to those who were prescribed LAI risperidone [103]. However, further research is clearly warranted to address the question whether or not treatment with LAI antipsychotic medication reduces the risk of nonadherence.

Tolerability

As mentioned above, some psychiatrists [93] and psychiatric nurses [104] consider LAI antipsychotics to be associated with a greater risk of side effects than oral medication. To determine whether pharmacokinetic differences actually affect the tolerability of oral versus LAI formulations of an antipsychotic, double-blind, randomized studies comparing bioequivalent doses of the two drugs would be needed. As bioequivalence would have to be determined by comparing receptor occupancy and plasma levels, such studies are very difficult to perform. However, a number of studies have compared the pharmacokinetic and side effect profiles of antipsychotics in oral and LAI forms. In this context, a metaanalysis by Adams and coworkers revealed an equivalent rate of EPS (defined as the need for anticholinergic medication) and tardive dyskinesia for FGAs in oral and LAI formulations [105]. Among NGAs, risperidone LAI (RLAI) has been shown to cause less fluctuations in plasma levels and a lower mean steady-state Cmax concentration than bioequivalent doses of oral risperidone [106]. This could account for the greater decrease from baseline prolactin levels found in patients switching to treatment with RLAI as compared to those who continue treatment with oral risperidone [107, 108]. It is unclear, however, whether this laboratory finding is of

clinical relevance. In patients treated with olanzapine, the pharmacokinetic differences between the oral and the LAI formulations seem to be irrelevant to the side effect profile [109]. However, when treating patients with olanzapine LAI (OLAI) one has to consider the risk of a post-injection syndrome, which presents with symptoms of an olanzapine overdose, occurs in less than 0.1% of injections, and appears to be unique to treatment with OLAI [110]. Therefore, after each injection of OLAI, patients have to be observed in a health care facility by an appropriately qualified person for a minimum period of 3 h. In addition, patients have to be accompanied home and should not drive or operate machinery on the day of injection. This clearly might have implications on a patient's attitude towards treatment with OLAI and secondarily on adherence. In addition, these protective measures infer a strain on the care system, thereby restricting the feasibility of managing patients with OLAI. Specialized depot clinics may help to overcome these hurdles.

Injection-related adverse effects that can occur with any injectable antipsychotic include injection-site pain and a range of local injection-site complications (swelling, induration, etc.). Next to appropriate injection technique, rotating injection sites, avoiding excessive injection volumes, and increasing the injection interval represent potential strategies to minimize these risks.

Conclusion

A number of circumstances and parties are involved in the multifaceted issue of adherence in schizophrenia. Next to the establishment of a solid therapeutic alliance they include pharmacological strategies providing optimal efficacy along with minimal adverse effects, the prescription of a once-daily dosage regimen, and monotherapy, if possible. In addition, the use of long-acting injectable antipsychotics allows the most reliable assessment of adherence, as patients who regularly show up to receive their injection have assured adherence, whereas patients who do not, are easily identified to be nonadherent.

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Non-Pharmacological Strategies to Enhance Adherence and Continuity of Care in Schizophrenia

Antonio Vita, Stefano Barlati and Emilio Sacchetti

Introduction

There is wide agreement that a major problem limiting success in the treatment of patients with serious mental illnesses, including schizophrenia, is poor adherence to prescribed medication regimens [1]. Long-term adherence to antipsychotic therapy is the cornerstone of contemporary management of psychosis, and patients who stop therapy have a markedly increased risk of relapse. Nonadherence with medication treatment is common but difficult to detect in patients with schizophrenia, almost half of whom take less than 70 % of prescribed doses [2]. The consequences of nonadherence can be devastating for patients and their families in terms of personal suffering, reduced quality of life as well as for society

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in general due to direct costs of healthcare, and loss of income [3]. Nonadherence is associated with poorer functional outcomes, including greater risks of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimization, suicide, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems [1, 4–7].

Despite the widespread nature and serious consequences of nonadherence to antipsychotic medication regimens, there is an evidence that physicians may not be aware when their patients discontinue their medications and that they overestimate their patients' adherence [1].

Interventions able to improve medication adherence in patients with schizophrenia would be beneficial in maximizing treatment outcomes with antipsychotics.

Studies that have specifically investigated adherence to psychiatric medications vary in the definitions of adherence and methodology used, making interpretation of results sometimes difficult. Numerous strategies have been proposed for improving adherence to treatment in patients with schizophrenia. The most successful strategies used a combination of educational, affective, and behavioral approaches. Interventions to improve adherence include encouraging acceptance of the illness, drawing analogies with treatment for chronic medical disease, and involving the patient in decision making. Clinicians must remain nonjudgmental, encouraging patients to disclose problems with adherence, and anticipating that improvement in adherence may require a prolonged effort [3, 8–11].

Factors Influencing (Non)Adherence in Schizophrenia

Medication taking is a complex health behavior that is affected by multiple factors that include treatment efficacy, side effects, clinician characteristics, treatment, illness beliefs, and sociodemographic factors [12]. Nonadherence can be viewed as either inadvertent or intentional [13]. Involuntary nonadherence occurs when signs or symptoms get in the way of taking medication (e.g., cognitive deficits), while intentional nonadherence results from a conscious decision on the part of the patient to discontinue medication. Unintentional dosage deviations and irregular adherence may further erode insight and therapeutic alliance resulting in the intentional discontinuation of antipsychotic treatment. Different interventions may be needed to address these different types of nonadherence [13].

The most common reason people do not take medication they intend to take is that they simply forget. This problem is compounded by the memory difficulties experienced by many patients with schizophrenia [14]. Furthermore, complex medication regimens are more difficult for people with schizophrenia to follow because of other cognitive problems, such as conceptual disorganization or inability to plan ahead [15, 16].

Patients with schizophrenia may not adhere to their prescribed medication regimen for several reasons (Table 1), including the following: illness awareness (lack of insight into illness, distorted, and ambiguous beliefs about treatment); psychopathology (psychotic symptoms, negative symptoms, and cognitive

Table 1 Factors influencing adherence to treatment in schizophrenia

Patient's related factors:
• Cognitive dysfunction
• Disorganization
• Lack of insight
• Personal history of nonadherence to treatment
• Health Belief Model:
(a) inadequate perceived efficacy
(b) attitude and subjective response to medication
(c) attitude and subjective response to side effects
• Alcohol and drugs abuse
Non patient's related factors:
• Complex pattern of pharmacotherapy
• Treatment's side effects (EPSs, weight gain, etc.)
• Lack of family and social support
• Family and cultural Health Belief Model
• Lack of supervision
• Limited access to services
• Lack of continuity of care
• Poor therapeutic alliance
• Stigma

EPS: Extrapyramidal Symptoms

impairment); medication-related aspects (lack of early therapeutic response or inefficacy of antipsychotic medication, medication side effects, route of administration and dosing strategies); environmental factors (family and social support); lack of access to medications; substance abuse; therapeutic alliance [3, 10, 17–20].

Interventions to Enhance Adherence: Research and Clinical Evidence

Although antipsychotic medications are the mainstay of treatment for schizophrenia, pharmacotherapy alone produces only limited improvement in negative symptoms, cognitive functions, social functioning, and quality of life [2]. Additionally, many patients continue to suffer from persistent positive symptoms and relapses particularly when they fail to adhere to prescribed medications. This

underlines the need for multimodal care including psychosocial therapies as adjuncts to antipsychotic medications to help alleviate symptoms and to improve adherence, social functioning, and quality of life [21, 22].

Despite the growing acceptance that medication nonadherence is a significant public health issue associated with financial, social, and illness costs, there is a limited amount of rigorous research on the use of specific interventions to target the problem. The available literature describes interventions of various types that have been utilized in schizophrenia. Some studies have specifically measured medication adherence as a primary outcome (primary outcome studies), while others described psychosocial interventions not used directly to address medication nonadherence, but that reported the effect of the intervention on adherence as a secondary outcome measure or as incidental finding (secondary outcome studies). Although the former provide more robust evidence, both types of study will be reviewed to give as much information as possible for translation into clinical practice [23]. Given the magnitude and importance of poor adherence to medication regimens, the WHO has published an evidence-based guide for clinicians, health care managers, and policymakers to improve strategies of medication adherence [24].

Several nonpharmacological strategies to enhance adherence in schizophrenia have been investigated. They include education sessions, memory aids, motivational interviewing, and cognitive behavioral approaches such as adherence or compliance therapy. Other suggestions such as optimizing therapy, for example by simplifying the regimen and considering side effect profiles with respect to individual patient characteristics, as well as fostering a good relationship between the patient and the healthcare professional, have been repeatedly mentioned. Studies demonstrate that no single strategy is effective for all patients and that a multidisciplinary approach customized to the patient's individual needs results in improved adherence rates [3, 8–10, 17, 23, 25–27].

Experts' recommendations reflect also the importance of individually tailoring medication regimens to improve adherence. It is crucial to select interventions that are likely to help eliminate the barriers that are interfering with adherence in the specific patient. Likewise, clinicians should keep in mind that the ultimate goal of any intervention is not medication adherence per se, but achieving the best possible outcomes for the patient [10, 28].

This systematic literature review focuses on studies examining psychosocial interventions to improve adherence to antipsychotic medications in patients with schizophrenia as a primary or a secondary outcome. Electronic searches were performed in the PubMed database and all studies published until April 2012 were included, without any language restriction. We found many kinds of psychosocial and programmatic interventions strategies for addressing adherence problems in schizophrenia that could have promising implications for clinical practice.

Comprehensive Review of Psychosocial and Programmatic Interventions to Enhance Adherence to Antipsychotic Medication in Schizophrenia

All the interventions and the strategies to improve adherence to antipsychotic medication in schizophrenia reviewed in this chapter are listed in Tables 2 and 3.

Psychoeducation

Psychoeducational interventions provide information to patients and family members about the disorder, its treatment, and strategies to cope with schizophrenia [2]. An extensive body of literature has accumulated regarding the efficacy of these interventions.

Meta-analyses [29–32] suggest that these interventions reduce high EE among relatives, and decrease relapse and rehospitalization rates. In general, interventions that include family members are more effective [33, 34].

(i) *Patient psychoeducation* involves strategies (e.g., individual and group counseling, use of written or audiovisual materials) to teach patients about their illness, medication and their side effects, and relapse prevention. Studies of psychoeducation in schizophrenia have used a range of interventions, but the majority has focused primarily on dissemination of knowledge about schizophrenia and treatment options to achieve medication adherence without specific action on attitudinal and behavioral change.
Seltzer et al. [35] described a cohort study of 67 inpatients with schizophrenia (44), bipolar disorder (16), and unipolar depression (7), allocated either to a control condition or to a psychoeducation programe consisting of nine lectures about their disorder and its pharmacological treatment, combined with behavioral reinforcement for desirable medication routines. Due to the inclusion of this latter approach, Zygmunt et al. [25] suggested that this was not a purely educational intervention as it contained elements of behavior modification. At the 5-month follow-up, it was found that the intervention group had a nonadherence rate of 6 % according to urine test and 9 % according to pill counts, whereas the control group showed rates of 25 and 66 %, respectively. The study has been criticized because of a substantial dropout rate both in the intervention and in the comparison group, which raised concerns about possible attrition bias. Brown et al. [36] randomly assigned 30 patients to receive one of four interventions: verbal information about their medication but not about side effects; verbal and written information about their medication but not side effects; verbal information about medication and side effects; or verbal and written information about medication and side effects. Results showed that although patients' knowledge about their medication improved with the interventions, this failed to translate into any change in adherence.

Table 2 General and tailored strategies to optimize adherence to treatment

Patient's related strategies:
• Assess limited illness insight
• Assess negative attitude toward taking medication
• Consider patient's view point, beliefs, and perspectives
• Recover any data and information to assess the adherence degree
• Cognitive remediation strategies
• Environmental supports
• Cognitive behavior strategies
• Patient's psychoeducation
Non Patient's related strategies:
• Simplify the drug regimen
• Maximize the effectiveness of pharmacotherapy
• Minimize pharmacological side effects when possible
• Family psychoeducation
• Involve family members
• Increase social support
• Supervision
• Assess environmental barriers
• Improve access to services
• Facilitate continuity of care
• Work on the treatment alliance
• Work on stigma and cultural beliefs

References [37, 38] reported that extended courses of group psychoeducation (35–75 sessions) did not significantly change adherence levels.

A further review by Dolder et al. [8] showed that only one of four educational interventions improved adherence.

Other studies found that psychoeducation used alone is not effective in improving medication adherence in schizophrenia [34].

In a randomized controlled study Maurel et al. [39] conclude that pharmacoeducation can reduce hospital stays of patients with schizophrenia and schizoaffective disorders, as well as improve their clinical and functional state, through better compliance.

In 2011 a Cochrane Database systematic review was made available, including a total of 5142 participants (mostly inpatients) from 44 trials

Table 3 Nonpharmacological interventions to enhance adherence to treatment in schizophrenia

Psychoeducation:
(i) Patient psychoeducation
(ii) Family psychoeducation
Behavior and Cognitive Interventions:
(i) Behavioral Interventions
(ii) Cognitive-Behavioral Interventions:
• Compliance Therapy
• Adherence Therapy
• Adherence-Coping Education
• Treatment Adherence Therapy
(iii) Health Belief Model
Medication Monitoring/Environmental Supports:
• Cognitive Adaptation Training
• Pharmacy-Based Intervention
• Short Message Service
• Telephone Medication Management
• Telephone Intervention Problem Solving
• Technology Aided Relapse Prevention Program
Community Interventions:
(i) Assertive Community Treatment
(ii) Case Management
Psychosocial interventions additional to pharmacological treatments
More frequent and/or longer visits
Symptom/side effect monitoring
Multifaceted/mixed-modality interventions

conducted between 1988 and 2009 (median study duration ~12 weeks, risk of bias—moderate). Authors found that incidence of noncompliance was lower in the psychoeducation group in the short term; this finding holds for the medium and long term. Relapse appeared to be lower in the psychoeducation group. They concluded that psychoeducation did reduce relapse, readmission, and encourage medication compliance, as well as reduce the length of hospital stay at least in these hospital-based studies. However, they also indicated that the true size of effect is likely to be less than demonstrated in this review—but, nevertheless, some sort of psychoeducation could be clinically effective and potentially cost beneficial [40].

(ii) *Family psychoeducation* Family psychoeducation has been shown to reduce relapse rates and facilitate recovery in persons with mental illness [41]. Psychoeducation for patients with schizophrenia that includes family members has been found to be more effective in reducing symptoms and preventing relapse than psychoeducation involving the patient alone [8, 34].

A trial by Xiang et al. [42] investigated family therapy in a rural province in China and showed significant benefits from this approach. The intervention group ($n = 36$) received a teaching program designed to provide family members with a basic knowledge of mental disorders and their treatment. The aim was to allow family members to understand the patient and his disorder and to understand how to care for the patient physically and psychologically. The intervention used family visits, workshops, and monthly supervision. At 4 months the rates of full adherence (patients were receiving a depot injection) were significantly improved in the intervention group (47 %) versus the control group (15 %), and the rates of full and partial adherence combined were 75 and 34 % in the intervention and control groups, respectively.

Two other studies showed positive results. In a rural area in China, Ran et al. [43] carried out a cluster randomized trial with 357 participants, in which three groups were compared. Intervention groups received depot medication, but one received in addition a monthly psychoeducational family intervention. After 9 months, 35 % of patients in the combined treatment group maintained regular treatment, in comparison with 32 % in the depot-only group and 5 % in the control group. The rates of patients who did not comply with treatment at all were 2 % in the combined group, 27 % in the depot group and 50 % in the control group, with accordingly increasing rates of relapse.

In a controlled trial, Chan et al. [44] investigated a psychoeducational program for patients and family caregivers in the urban area of Hong Kong. 73 patients were included and the intervention consisted of 10 family sessions of psychoeducation within a period of 3 months. One month after completion of the interventions, and again 6 months later, significant differences in favor of the intervention group were reported on adherence to medication, as measured by the ROMI, mental status, insight into illness in patients, self-efficacy, satisfaction, and perception of family burden in caregivers, yet these benefits were not sustained after 12 months of follow-up. They concluded that psychoeducation should be offered as an ongoing intervention.

Findings by the Munich Psychosis Information Project Study are described in the following two studies. In the first [45], the authors examined whether psychoeducational groups for patients with schizophrenia and their families could reduce rehospitalization rates and improve compliance 236 inpatients who met DSM-III-R criteria for schizophrenia or schizoaffective disorder and who had regular contact with at least one relative or other key person were randomly assigned to one of two treatment conditions. In the intervention condition, patients and their relatives were encouraged to attend psychoeducational groups over a period of 4–5 months. The patients and 'relatives' psychoeducational programs were separate, and each consisted of eight

sessions. Outcomes were compared over 12 and 24-month follow-up periods. The rehospitalization rate after 12 and 24 months in patients who attended psychoeducational groups was significantly lower and degree of compliance higher than those obtained in patients receiving routine care ($P < 0.05$). The results suggest that a relatively brief intervention of 8 psychoeducational sessions with systematic family involvement in simultaneous groups can considerably improve the treatment of schizophrenia.

In the second intervention study [46], the same research group investigated the long-term effects of psychoeducation over a period of 7 years in regard to rehospitalization rates and hospital days. Of 101 patients with DSM-III-R or ICD-9 schizophrenia randomly allocated to either the intervention or the control group, 48 patients were available for follow-up after 7 years. Main outcome measures were rehospitalization rate, number of intervening hospital days, compliance, and mean number of consumed CPZ units. Seven years after index discharge, the rate of rehospitalization was 54 % in the intervention group and 88 % in the control group. In the intervening period, the mean number of hospital days spent in a psychiatric hospital was 75 in the intervention group and 225 in the control group ($P < 0.05$). The mean number of consumed CPZ units was 354 in the intervention and 267 in the control group. Therefore, 7 years after psychoeducational group therapy, significant effects on the long-term course of the illness could be found.

In a more recent study [47] it has been investigated whether a culturally adapted, MFG, based on psychoeducation and skills training, would increase medication adherence and decrease psychiatric hospitalizations for Spanish-speaking Mexican-Americans with schizophrenia. There are 174 Mexican-American adults with schizophrenia-spectrum disorder with a recent exacerbation of psychotic symptoms and their key relatives were studied in a 3-arm, randomized controlled trial of MFG therapy focused on improving medication adherence. Assessments occurred at baseline and at 4, 8, 12, 18, and 24 months. Patients participated in one of two MFGs (culturally modified MFG-adherence or MFG-standard) or treatment as usual. Groups convened twice a month in 90-minute sessions for 1 year. At the end of the 1-year treatment, MFG-adherence was associated with higher medication adherence than MFG-standard or treatment as usual ($P = 0.003$). The MFG-adherence participants were less likely to be hospitalized than those in MFG-standard ($P = 0.04$) and treatment as usual alone ($P < 0.001$). Authors concluded that MFG therapy specifically tailored to improve medication adherence is associated with improved outcome for Mexican-American adults with schizophrenia-spectrum disorders.

On the other hand, other studies utilizing psychoeducation and family interventions failed to demonstrate an improvement in medication adherence [48, 49], as did an inpatient family intervention [50] and a family relapse prevention program [51].

A recent meta-analysis [34] has evaluated short and long-term efficacy of psychoeducation with and without inclusion of families with regard to relapse, symptom reduction, knowledge, medication adherence, and functioning. Randomized controlled trials comparing psychoeducation to standard care or nonspecific interventions were included. Independent of treatment modality, psychoeducation produced a medium effect size at post-treatment for relapse and a small effect size for knowledge. Psychoeducation had no effect on symptoms, functioning, and medication adherence. Effect sizes for relapse and rehospitalization remained significant for 12 months after treatment but failed to reach significance for longer follow-up periods. Interventions that included families were more effective in reducing symptoms and preventing relapse at 7–12 month follow-up. The most interesting finding is that psychoeducation offered solely to patients was ineffective. It was concluded that the additional effort of integrating families in psychoeducation is worthwhile, while patient-focused interventions alone need further improvement and research.

A 2010-Cochrane review estimated the effects of family psychosocial interventions in community settings for people with schizophrenia or schizophrenia-like conditions compared with standard care. Family intervention may decrease the frequency of relapse and may also reduce hospital admissions and encourage compliance with medication, but it does not consistently affect the tendency of individuals/families to drop out of care. Authors concluded that family interventions may reduce the number of relapse events and hospitalizations, but they also underlined that treatment effects of these trials may have been overestimated [52].

Behavioral and Cognitive-Behavioral Interventions

CBT seeks to help patients rationally appraise their experience of symptoms of disease and how they respond to them, thereby reducing symptoms and preventing relapse [53, 54]. Although CBT is recommended as a standard of care for persons with schizophrenia [55, 56], data from pragmatic studies suggest that its benefits are modest at best [57, 58]. We will analyze separately behavioral and cognitive-behavioral interventions (Table 4).

(i) *Behavioral Interventions* assume that behaviors are acquired through learning and conditioning and can be modified by targeting, shaping, rewarding, or reinforcing specific behavioral patterns. Interventions include skills building, practising activities, behavioral modeling, and reinforcement strategies. Behavioral tailoring involves developing natural prompts by fitting the taking of medication into each person's usual routine.

A number of studies have shown behavioral interventions to be successful in improving medication adherence.

Table 4 Cognitive and behavioral strategies to enhance adherence

Behavioral strategies:
• Skills building
• Behavioral modeling
• Behavioral prompts
• Rewarding strategies
• Reinforcement strategies
• Monitoring
Cognitive strategies:
• Assessing patient perspective and beliefs
• Identifying negative attitude toward medication and illness
• Motivational interventions
• Addressing and changing negative attitude toward medication and illness
• Modifying negative automatic thoughts, re-evaluate beliefs about medication

Eckman et al. [59] investigated a behavioral program in improving adherence and medication management skills in 160 outpatients with schizophrenia. Patients followed a structured module in groups for about 3 h per week over 4 months. Adherence improved significantly from about 60 % preintervention to 80 % post-intervention.

Boczkowski et al. [60] randomly assigned 36 males with schizophrenia to behavioral training, didactic psychoeducation, or standard treatment. The behavioral intervention consisted of patients being told the importance of adhering to medication and each participant was helped to tailor the prescribed regimen so that it was better adapted to their personal habits and routines. This involved identifying a highly visible location for placement of medications and pairing the daily medication intake with specific routine behaviors. At a 3-month follow-up, there was a significant improvement in the behavioral intervention group compared with the other two groups. Totally, 8 out of 11 patients who had received behavioral therapy showed adherence with 80 % or more of their medication, whereas only three out of 11 in the psychoeducation intervention group showed such levels.

Cramer and Rosenheck [61] described a randomized controlled trial of 60 patients allocated to usual treatment or to the MUSE program that teaches simple techniques of how to remember daily medication doses to patients with severe mental disorders. The intervention consisted of an initial session of 15 min where the patient was taught to develop cues to remember the dose times. The intervention utilized electronic monitoring pill bottles with special caps that display the date and time of each bottle opening. Results showed significant improvement in the intervention group. The mean 1-month adherence rate was 81 % in the

intervention group and 68 % in the control group, at 6 months the rate was 76 and 57 %, respectively.

Razali et al. [62] studied the effectiveness of culturally modified behavioral family therapy compared with a standard version of behavioral family therapy in 166 individuals. Post-randomization, there were 74 subjects in the culturally modified intervention group and 69 in the behavioral family therapy group. Adherence was measured globally as a percentage of the total prescribed dosages actually taken during the previous 6 months. At follow-up, 73 % in the group receiving culturally modified therapy as compared to 59 % in the control group were adherent with 90 % of their prescribed medication. At 1 year, rates were 85 and 55 %, respectively.

(ii) *Cognitive-Behavioral Interventions* are focused on understanding patients' perception of their problems and treatment. One of the major challenges in addressing the patient's attitude toward medication is the degree to which patients with schizophrenia avoid acknowledging that they have an illness or need treatment in the first place. For patients who do not believe they need medication, environmental supports alone will not address the problem, but CBT may help. Because CBT focuses on changing attitudes, it may be ideally suited to addressing adherence problems in patients who do not believe they are ill. CBT include assessing patient perspective, examining evidence, and rolling with resistance. Rolling with resistance means not challenging the patient's resistance to taking medication but exploring this resistance to better understand the patient's viewpoint and help the patient re-evaluate beliefs about medication. CBT therapists help patients identify and modify negative automatic thoughts about medications and use guided discovery to help strengthen patients' belief that taking medication is associated with staying well and achieving goals. The support for CBT to address lack of insight reflects findings from controlled trials showing that CBT significantly improves insight into the need for treatment and that even a brief CBT intervention can significantly improve symptomatology and insight [2, 63].

In schizophrenia, CBT to improve adherence often incorporates motivational interviewing techniques. First developed for use in addiction treatment, these techniques assess patients' motivation to make changes in behavior related to adherence.

Lecompte and Pelc [64] tested a cognitive behavioral program targeted at changing adherence patterns through the use of five therapeutic strategies: engagement, psychoeducation, identifying prodromal symptoms, developing coping strategies and strategies for reinforcing adherence behavior, and correcting false beliefs about medication. There are 64 nonadherent patients with psychosis were randomly assigned to receive either the active intervention or a control treatment of unstructured conversation. The primary outcome measure was the duration of hospitalizations 1 year before and 1 year after the intervention, which the authors argued was a useful indirect measure of adherence. Patients receiving the cognitive behavioral intervention spent significantly less time in hospital in the year after as compared to the year before the intervention, but no significant difference was found relative to the

control group. Although these findings suggest the intervention is beneficial, it is not certain that this improvement can be attributed solely to improved adherence.

Motivational Interviewing has been defined as "a directive client centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence" [65]. Although behavioral analysis is used, motivational interviewing does not try to force the person into accepting the evidence of advantages of a new behavior but considers the value of letting persons progressively discover advantages and disadvantages of their behavior for themselves.

Hayward et al. [66] used an intervention of medication self-management based on motivational interviewing aiming to allow patients and clinicians to work collaboratively to examine medication issues. Twenty-one inpatients received three 30-min sessions of either medication self-management or nondirective discussion on any issue except medication. The pilot work showed trends in favor of the intervention group with regard to adherence and attitudes toward treatment but none reached statistical significance.

This led to the development of the longer, more structured intervention CT [67, 68] which modified motivational interviewing techniques to give particular attention to the therapeutic relationship and to make the approach useful with patients suffering from psychosis and combined this with cognitive behavioral techniques. CT is a CBT intervention that targets adherence issues and incorporates psychoeducation and motivational interviewing to help patients understand the connection between relapse and medication nonadherence to improve motivation for taking medication.

The therapy is described in detail in a treatment manual [69]. The key techniques are those of reflective listening, regular summarizing, inductive questioning, exploring ambivalence, developing discrepancy between present behavior and broader goals, and using normalizing rationales. The intervention is divided into three phases that acknowledge that readiness to change is on a continuum. Phase 1 deals with patients' experiences of treatment by helping them review their illness history. In phase 2 the common concerns about treatment are discussed and the "good" and the "bad things" about treatment are explored. Phase 3 deals with long-term prevention and strategies for avoiding relapse. Despite its name, CT appears to fit with a concordance model, involving patients in making decisions that are right for them, rather than trying to get them to be obedient to professional advice.

In a small-scale study, Kemp et al. [68] found that CT significantly improved insight, attitudes toward treatment, and adherence in patients with schizophrenia. The same research group reported a randomized controlled trial of 74 patients with psychosis allocated to 4–6 sessions of CT versus 4–6 sessions of supportive counseling [70]. Results demonstrated a significant effect on adherence in the intervention group as compared to the control group immediately post-treatment and at an 18-month follow-up. The improvements in compliance did result in enhanced community tenure, with patients in the CT group taking longer to relapse than those receiving nonspecific counseling. CT is effective in enhancing concordance and reducing the risk of relapse. There is also emerging evidence that

after training in medication management, mental health nurses are able to deliver compliance therapy to people with a diagnosis of schizophrenia [71].

In contrast to the above studies, O'Donnell et al. [72] conducted a randomized controlled trial comparing CT with nonspecific counseling in a 1-year study of 56 inpatients with schizophrenia. No effect of CT over a control group was identified. The study did show that attitudes to treatment at baseline predicted adherence at 1 year, thus suggesting early identification of attitudes toward medication may be useful in clinical practice. Noticeably, this study had a longer period of follow-up (1 year), while the two previous studies had shorter periods of follow-up assessment (3 and 6 months). Although the study by Kemp et al. had further assessments at 12 and 18 months, their booster doses of the intervention at 3, 6, and 12 months may have influenced its long-term outcome.

Byerly et al. [73] evaluated the efficacy of CT when delivered to outpatients with schizophrenia or schizoaffective disorder. Thirty patients with schizophrenia or schizoaffective disorder were recruited from urban psychiatric outpatient clinics in an open trial of CT. The primary outcome was electronically measured antipsychotic medication adherence. Adherence data were analyzed for effects during an initial treatment period (month −1 to +1) and a subsequent 5-month follow-up period. Secondary outcome measures included clinician and patient ratings of adherence, symptoms, insight, and attitudes toward medication treatment. Patient ratings of adherence improved during the month −1 to +1 period, but not in the subsequent 5-month follow-up. Authors found that CT was not associated with improvements in antipsychotic medication adherence and they concluded that outpatients with schizophrenia or schizoaffective disorder did not benefit from CT schizophrenia.

In a 2006 Cochrane review on CT, McIntosh et al. [74] assessed systematically the effects of this intervention on antipsychotic medication adherence in schizophrenia. Authors concluded that there is no clear evidence to suggest that CT is beneficial for people with schizophrenia and related syndromes, and that more randomized controlled studies were needed in order to fully examine this intervention.

CT was slightly modified into AT, a brief individual cognitive behavioral approach [75]. The AT manual (http://www.adherencetherapy.com) describes a collaborative, patient-centered phased approach to promote treatment adherence, patient choice, and shared decision-making in subjects affected by schizophrenia. Techniques derived from cognitive behavioral therapy (e.g., testing out beliefs about treatment) and motivational interviewing (e.g., exploring patient ambivalence toward treatment) are used to enhance adherence to a shared treatment plan focused on medication adherence and illness management. The key therapeutic techniques used are exchanging information, developing discrepancy, and effectively dealing with resistance. The phases of AT are engagement, assessment, rating of readiness to take medication, intervention, and evaluation working through in a flexible patient-centered way. The five key interventions from the core of the therapy phase include: (1) medication problem solving; (2) medication timeline; (3) exploring ambivalence; (4) discussing beliefs and concerns about

medication; and (5) using medication in the future. The aim of the therapy process is to achieve a joint decision about medication between the patient and therapist.

A study in Thailand [76] found that AT delivered by nurses who received intensive training significantly improved psychotic symptoms and attitude toward and satisfaction with medication. Thirty two patients with schizophrenia were randomly allocated to receive eight weekly sessions of AT or continue with their TAU. Patients were assessed at baseline and after 9 weeks. The primary outcome was overall psychotic symptoms. Secondary outcomes were general functioning, attitude toward and satisfaction with antipsychotic medication, and medication side effects. The findings indicated that patients who received AT significantly improved in attitude toward and satisfaction with medication compared with TAU.

A large European 52-week, single-blind, multicentre randomized controlled trial, with a small increase in the number of sessions (two extra sessions) and a more individually tailored structure, including 409 patients in four countries, did not find any differences between AT and a control group receiving an individual intervention of health education, nor were quality of life, or rates of patient-reported medication adherence different between groups. This effectiveness trial did not confirm any effect of AT in improving treatment adherence in people affected by schizophrenia with recent clinical instability, treated in ordinary clinical settings [75].

A further pragmatic, exploratory, single-masked trial, to explore the efficacy, acceptability, and satisfaction with AT was conducted in the USA, in a sample of people with schizophrenia [77]. Twenty six patients (12 experimental and 14 controls) were randomly allocated to receive eight weekly sessions of AT or continue with TAU. Patients were assessed at baseline and after therapy completion, while the primary outcome was psychiatric symptoms and the secondary outcome medication adherence. Patients receiving AT did not significantly improve in overall psychiatric symptomatology or in medication adherence compared with the TAU group at follow-up. The results indicated no significant difference between the AT and TAU groups on measures of severity of symptomatology and subjective evaluation of treatment, including medication adherence from baseline to follow-up after the completion of the intervention.

Another adaptation of CT is called *ACE*, which aims at enhancing insight and at promoting treatment adherence in patients with early psychosis. In a pilot study this intervention, consisting of 14 individual sessions, was tested against supportive therapy [78]. In a sample of 19 participants, perceived need for treatment and benefits of medication appeared to be better in patients with ACE shortly after intervention, compared to controls. However, no direct adherence rates were available and follow-up results are awaited.

Staring et al. [79] developed another treatment, *TAT*, whose intervention modules are tailored to the reasons for an individual's nonadherence. In a recent randomized controlled trial therapy they measured the effectiveness of TAT with regard to service engagement and medication adherence in 109 outpatients with psychotic disorders. TAT is an intervention based on an empirical–theoretical model, in which patient's determinants of nonadherence are taken into account. According to the

clusters of determinants of nonadherence, therapists choose the intervention tailored to each patient. The duration and number of sessions therefore varied according to the needs of the individual patient, in general, it took no more than 6 months. Most of the TAT therapists were trained psychiatric nurses. The study found that TAT may enhance service engagement (Cohen's $d = 0.48$) and medication adherence (Cohen's $d = 0.43$) more than TAU. The effects were smaller at 6-month follow-up, yet still statistically significant for medication adherence.

(iii) HBM summarizes the process by which the patient weighs the cost of treatment against benefits, assuming adherence to the treatment if the benefits are seen to be greater than the costs and risks [80–82]. The HBM is one of the most known model of behavior change and it has been developed to explain why people failed to take up disease prevention measures or screening tests before the onset of symptoms [80, 83]. The original model proposed that the likelihood of someone carrying out a particular health behavior (e.g., attending for screening) was a function of their personal beliefs about the perceived threat of the disease and an assessment of the risk/benefits of the recommended course of actions. The individual weighs up the perceived benefits of an action (e.g., taking medication might ease symptoms) against the perceived barriers to the action (e.g., fear of side effects or costs of the treatment). The HBM assumes that four main beliefs contribute to the likelihood of individuals adhering to their prescribed medication:

- perceived benefits of adherence (e.g., possibility of being symptom-free)
- perceived barriers to adherence (e.g., stigma or problems with side effects)
- perceived susceptibility to illness (e.g., a belief that they are likely to experience a relapse)
- perceived severity of the outcome (e.g., a belief that relapse would have negative consequences).

It is proposed that individuals are more likely to adhere to medication if the perceived threat of the illness (susceptibility and severity) is high and the perceived benefits of treatment exceed the perceived barriers.

Compliant patients consider the medication to be helpful in treating their illness and have a positive attitude toward medication [84–86]. Conversely, noncompliant patients see no reason for taking medication because they may not consider themselves to be ill, or they may see taking the medication as the wrong way to solve their problems [87–91].

The beliefs described are influenced by a number of modifying factors [92] such as:

- personality attributes (e.g., dysfunctional attitudes and health locus of control)
- influence of significant others (e.g., family and mental health professionals)
- cultural beliefs and context
- general health motivations
- general orientation toward medicine

The model also states that individuals need a prompt (a reminder either of the threat of the illness or the action that must be taken against it) before they will engage in health-related behaviors [93]. These "cues to action" may be internal,

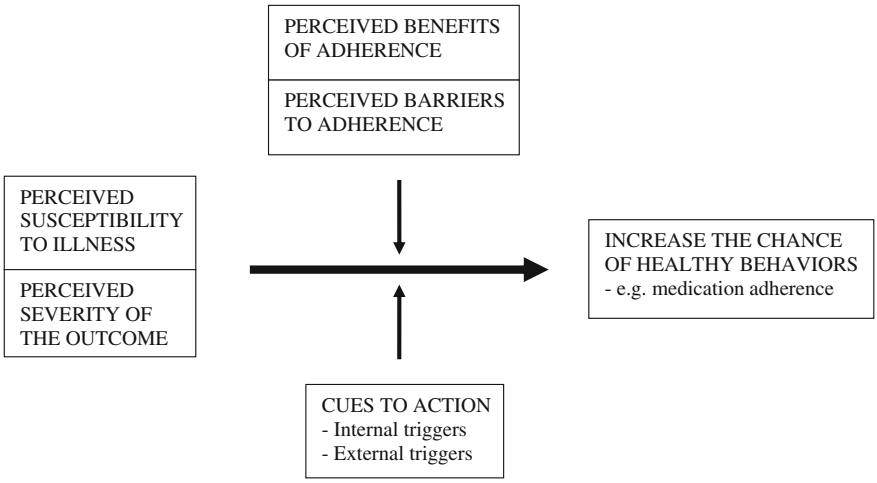

Fig. 1 Health belief model (HBM)

such as recognition of prodromal symptoms, alternatively, the cues may be external, such as statements made by others, or media references to illness or medication (Fig. 1).

This model emphasizes the collaboration between physician and patient in treatment decisions. The critical factor for successful management of adherence is creating an atmosphere where a nonadherent or potentially nonadherent patient does not feel disapproved and so he will be able to talk honestly about his concerns related to drug treatments and pattern of adherence [82].

The clinician needs to have a clear picture of the patient's cognitive representation of the illness. If patients acknowledge partial or total nonadherence, it is useful to try to decide whether this is unintentional or intentional. Un-intentional nonadherers tend to identify a higher number of perceived barriers to treatment. Most of these are practical rather than psychological. Intentional nonadherers often demonstrate more ambivalence about the perceived threat of the disorder and are probably less likely to acknowledge their nonadherence without prompting. In practice, it is likely that both groups will benefit from the behavioral interventions, but that the cognitive techniques will have a more obvious role with intentional nonadherers. The primary goal with unintentional nonadherers is to enhance cues to action and to minimize any real or perceived barriers to adherence [13].

The HBM posits that health behavior is a product of an implicit and subjective assessment of the relative costs and benefits of compliance in relation to personal goals and the constraints of everyday life. HBM has proven helpful in addressing adherence in medical illness, however, it must be used cautiously in patients with schizophrenia. Disease-related symptoms such as cognitive impairment and poor reality testing may limit a patient's ability to perceive the benefits of antipsychotic therapy. Since schizophrenia may disrupt illness perception and the capacity to

plan and act, consideration of the cognitive and motivational resources available to assess risk, and formulate action should be additional elements to take into account when dealing with patients suffering from schizophrenia [13, 84–91].

Patients affected by schizophrenia weigh the benefits of antipsychotic treatment such as symptom reduction with the associated costs of antipsychotic treatment such as side effects. Benefits of antipsychotic treatment are largely dependent on the patient's knowledge about illness and belief that the treatment may has a positive effect on the severity of their symptoms. The HBM emphasizes the patient's as opposed to the physician's understanding of illness and treatment [94]. Perceived benefits of treatment are largely dependent on the patient's illness awareness and insight. Insight has been one of the most common predictors of adherence problems [94, 95] and it is not necessarily found in all patients who are adherent with antipsychotics [96]. Most patients have some ambivalence about taking antipsychotic medications, all of which can be associated with unpleasant and, rarely, dangerous side effects. On the other hand, patients with good insight into their symptoms or illness may not perceive their prescribed medication as potentially or actually helpful. Patients who do experience troublesome or serious side effects may decide that these effects outweigh the benefits of medication. If a patient stops taking medication during the stable phase, he may feel better, with less sedation or other side effects. As a result, the patient may come to the false conclusion that the medication is not necessary or does not have benefits. Finally, people significant to the patient, including family and friends, may discourage the patient from taking medication or participating in other aspects of treatment.

HBM may help clinicians to develop methods to improve adherence. To help clinicians learn how to adapt CBT for assessing adherence attitudes, Velligan et al. [97] have developed a method called the HBD. The underlying concept of this interview approach is very simple. The authors believe that attitudes or beliefs cannot be changed before the clinician understands those attitudes and beliefs. Too often patients' perspective is interrupted by a well-meaning but ineffective lecture about the benefits of medication and the importance of adherence. In contrast, a major goal of the HBD approach is forcing the clinician to withhold any intervention or comment on adherence attitudes until those attitudes are fully understood [97].

Perkins [94] has modified the HBM in the context of schizophrenia and underlined the relevance of improving patient's assessment of the costs and benefits of treatment. This may require targeting a diverse area of risk factors for nonadherence such as poor insight, negative attitudes toward medications, substance abuse, and alliance with therapist. When clinicians detect the presence of any of these risk factors for nonadherence, strategies to address these issues and interventions to improve adherence should be implemented. Successful aspects of the interventions reviewed can be easily incorporated by clinicians to improve adherence with antipsychotic therapy such as, providing information about the purpose and potential side effects of medications (psychoeducation); helping patients to cognitively reframe negative attitudes and learn to become more effective

consumers (behavioral and affective); and simplifying regimens, teaching skills, and providing external cues such as medication reminder devices (behavioral) [8].

Perceived benefits of treatment also include the therapeutic relationship. The quality of the therapeutic relationship is related to medication adherence [98, 99]. In a cross-sectional and longitudinal adherence study with 162 patients, working alliance was most consistently related to medication adherence [100]. Patient satisfaction in the physician–patient relationship may lead to a greater willingness to follow the physician's advice independent of the level of insight of the patient.

Costs of treatment include the patient's perception of medication side effects. When patients perceive adverse effects as problematic or unacceptable they may lead to poor adherence. On the contrary patients will often continue to take medication despite unpleasant side effects if they perceive the benefits of medication as outweighing the disadvantages caused by side effects [101].

There are studies suggesting a correlation between dimensions of the HBM and adherence in schizophrenia.

Budd et al. [102] found an association between beliefs around susceptibility and adherence status, that is, those who did adhere to medication perceived themselves to be more susceptible to relapse than nonadherers. They conducted a study of the impact of the HBM in schizophrenia patients in Wales comparing 20 patients who had presented for, and accepted, depot antipsychotic medication at all scheduled appointments over the year prior to the study (compliers) with 20 patients who had failed to attend and/or accept medication for one-third or more of all scheduled appointments over the same period (noncompliers). The constructs of the HBM were evaluated using a HBQ [103, 104]. The authors found that scores on the susceptibility subscale had the greatest discriminatory power in distinguishing compliers from noncompliers. Scores on the severity and benefits subscales were significant in distinguishing between the two groups when tested in separate analyses, but were not significant when added to a model that already contained the susceptibility subscale.

Adams and Scott [105] explored the utility of the HBM in explaining medication adherence in subjects with severe and disabling mental disorders. Six well-established measuring instruments, with confirmed reliability and validity, were used to assess each component of the HBM and medication adherence in 39 hospital-treated subjects with severe mental illness. Highly adherent and partially adherent subjects differed significantly in their perception of illness severity, their beliefs about themselves and their control over the disorder, and their concerns about further hospitalization. Two components of the HBM (perceived severity of illness and perceived benefits of treatment) explained 43 % of the variance in adherence behavior. Although the study has a number of methodological limitations, the results suggest that clinical assessment of components of the HBM may improve the detection of patients at risk of medication nonadherence.

Fenton et al. [98] categorized the range of factors affecting adherence into patient-related, medication-related, environmental factors, and psychodynamic considerations. They identify patient-related factors as: demographic characteristics such as gender and ethnicity, illness characteristics such as age at onset and

duration of illness, illness severity and subtype (e.g., paranoid schizophrenia), cognition or memory, insight, other health beliefs (i.e., attitudes toward medication), subjective well-being, and alcohol and drug use. The medication-related factors reviewed were side effects, dosage, agent, route, and complexity of regimen. Environment factors considered were: family and social support, practical barriers (e.g., financial burden preventing patient from filling prescription), physician–patient relationship, attitude of staff, reinforcement, education, and memory enhancement. Psychodynamic considerations include: psychological meaning (e.g., feelings about the role of authority and control in the prescribing of medications) and psychological homeostasis (e.g., relationship between delusions and self-image). The analyses would also have been improved with inclusion of a measure of patients' attitudes toward their medication, their insight and general cognitive functioning [106], and perceptions of their quality of life. A positive view of psychiatric medications and patient insight has been shown to improve adherence [107]. These factors may be associated with the HBM, which Oehl et al. [108] suggest is a major determinant of adherence.

Although HBM may require modification in disorders like schizophrenia [109, 110], it should facilitate a shift in perspective: rather than viewing noncompliance as the patient's problem, it is redefined as an indication that the therapeutic regimen is not assisting the individual patient to achieve his goals. Few studies have been done, but one small study demonstrated that patients with schizophrenia lack consistently coherent beliefs about their health, and beliefs may vary with mental status [111]. Persons with medical illnesses distinguish between themselves and their illness, whereas persons with schizophrenia often describe psychotic symptoms as part of themselves. Although many may not believe that they are ill, patients who acknowledge mental illness often do not view themselves as an entity separate from their mental illness. Recovery models, which address adherence, fall short because patients may not be able to conceptualize recovery or the need to recover because they cannot conceptualize their illness or a need to be well. Kinderman et al. [111] advocated more research into health beliefs in schizophrenia and speculated that assessing the patient's concept of psychotic episodes may be more beneficial and fit better with the patient's concept of his difficulties.

Medication Monitoring/Environmental Supports

Many studies focused on specific support for cognitive impairment, based on the assumption that nonadherence in patients with schizophrenia may be partly due to cognitive difficulties in attention or memory [17]. One approach to overcome these problems is to teach patients how to use devices to help take their medication correctly [10]. Medication monitoring and environmental supports include dispensing doses, directly observing medication taking, providing environmental supports at home as reminders to take medications and fill prescriptions, helping people deal with practical barriers to come to appointments or refilling

prescriptions. A wide range of pill-organizing boxes is available for storing medications in separate compartments based on the day and time-of-day they are supposed to be taken. Pill organizers may contain the pills for a single day (which can be easily carried around in a purse or pocket), a week, or a month. When a prescription is filled, the patient, nurse, or pharmacy fills the pill organizer so that all of the pills that need to be taken at a particular time of day are stored together. Pill organizers are useful for keeping track of what medications need to be taken and when, but they often don't address the problem of people simply forgetting to take their medication. Many patients find alarms are effective to serve this function. Some pill organizers also contain alarms or reminder chimes that can be set to prompt people to take medication. Other patients may find it more convenient to set a reminder alarm on something they frequently carry with them, such as a wrist watch, cell phone, MP3 player, or electronic scheduler. The experts considered medication monitoring/environmental supports as the first-line choice for addressing nonadherence in patients with cognitive deficits. Clinicians should note that environmental supports are not likely to be used unless they are customized for the individual patient and set up in the home environment [112, 113].

A program called CAT appears to be a promising strategy to improve adherence [114–116]. CAT is a manual-driven series of environmental supports designed to bypass problems in attention, memory, and executive functions, cue and sequence appropriate behaviors, and discourage inappropriate behavior at home. It is an intervention employing a series of compensatory strategies based on neuropsychological, behavioral, and occupational therapy principles. Training includes a neuropsychological assessment to examine the level of executive functioning, attention, and memory. Cognitive adaptation focused on medication adherence uses individually tailored environmental supports (e.g., signs, checklists, alarms, electronic cuing devices, organization of belongings) to cue adaptive behavior in the patient's own home environment and help compensate for cognitive deficits. It also addresses logistic issues related to obtaining appointments. CAT supports are offered to the client during home visits on a weekly basis to address specific problems. An extensive intervention (full-CAT) tackling several aspects of functioning (poor hygiene, grooming, care of living quarters, leisure skills, social and role performance, and medication adherence) was compared with cognitive adaptation focusing only on adherence to medication and appointments (Pharm-CAT) and with a control group receiving TAU, in a randomized trial with 105 participants [28]. The intervention was carried out for a period of 9 months with a follow-up of 6 months. It resulted in significantly better adherence to medication for both intervention groups, as measured by unannounced pill counts. Average adherence rates were roughly 80 % in the intervention groups during the 15 months of the intervention and follow-up, compared to 60 % in the TAU group. The percentage of relapse for both intervention groups was 35 % against 81 % for the control group. This effect was maintained for 6 months after the intervention was completed. Outcomes of social and occupational functioning improved only with full-CAT, with a deterioration after the intervention stopped, suggesting that these aspects probably ask for continued intervention. The authors concluded that targeted

supports can improve adherence and reduce relapse rates, but that comprehensive supports targeting multiple domains are necessary to improve functional outcomes.

In another study Velligan et al. [117] examined the short-term efficacy of CAT and GES to improve target behaviors in individuals with schizophrenia. GES include hygiene supplies, pill containers, and calendars offered to individuals at the time of their regular clinic visits. In GES, clients are expected to set up the supports on their own, supported by a tape recording of the therapist discussing where and how to use the supports in the home environment. One hundred and twenty outpatients with schizophrenia or schizoaffective disorder were randomized into one of the following three treatment groups: (1) CAT—individualized supports established on weekly visits in the clients' homes; (2) GES—a generic group of environmental supports provided at a routine clinic visit; and (3) TAU. Global level of functional outcome and target behaviors, including medication adherence, were assessed at baseline and after 3 months. Patients in both CAT and GES had better scores on global functional outcome at 3 months than those in TAU; on the other hand, patients in CAT were more likely to improve on target behaviors, including medication adherence, than those in GES.

Another study to compensate for attention and memory problems used a *Pharmacy-Based Intervention*, called Meds-Help Intervention [118]. A low-complexity pharmacy-based intervention for patients with severe mental illness was developed, designed to reduce medication access barriers and to provide ''cues to action'' to help patients remember to refill prescriptions and take scheduled doses. In a randomized controlled trial with 118 participants of which 67 % had a schizophrenia-spectrum disorder, the intervention group received unit-of-dose packaging for all the medication they were taking and a packaging education session; refill reminders were mailed 2 weeks before the scheduled refill dates. Also, clinicians received notification when a patient failed to collect his antipsychotic prescriptions. Statistically significant improvements in MPR were observed in the intervention group after 6 and 12 months, compared with a control group that received care as usual. When a more stringent measure of adherence was used, by combination of a MPR of greater than 80 % with a positive subjective assessment of adherence and a blood test indicating the presence of some antipsychotics, 50 % of the intervention group fulfilled the criteria of adherence after 6 months versus 17 % in the control group. Authors conclude that this low-complexity pharmacy-based intervention is feasible in clinical practice and increased antipsychotic adherence among patients with severe mental illness.

Recent research focused on telephonic interventions and new technologies to assess and enhance adherence and treatment outcomes in persons diagnosed with schizophrenia. Reminders with SMS text messages in one study [119] did not lead to better adherence. These authors evaluated the efficacy of SMS text messages to compensate for the effects of cognitive impairments in daily life. Sixty two people with schizophrenia or related psychotic disorders were included in the study. Patients were prompted with SMS text messages to improve their everyday functioning. The overall percentage of goals achieved increased with prompting, but performance dropped to baseline level after withdrawing the prompts. Keeping

appointments with mental health workers and carrying out leisure activities increased with prompting, while medication adherence and attendance at training sessions remained unchanged.

The TMM program was designed as a brief (no more than 10 min), weekly telephone-based intervention with the following goals: (1) provide verbal reinforcement for positive self-care behaviors (e.g., adhering to treatment regimen and clinic attendance); (2) encourage frank discussions about treatment- related issues; (3) validate participant's medication and treatment experience; (4) assist problem solving on strategies to enhance self-care. TMM was an adjunctive service that ultimately aimed to enhance communication, insight into illness, attitudes and knowledge about treatment, medication adherence, treatment satisfaction, and decrease treatment side effects. A randomized demonstration study was conducted at a large, urban community mental health center to examine the feasibility and costs associated with TMM and to assess the outcomes of such an approach [120]. A total of 32 persons affected by schizophrenia-spectrum disorder were enrolled. Fourteen were randomized into the control group and 18 into the TMM condition. Results suggest that TMM was acceptable to patients and could be feasibly delivered. Although the direction of positive effects was consistently in favor of the TMM intervention, no apparent differences in treatment adherence were found, despite positive changes in other areas (e.g., insight and staff relationships) found to be associated with adherence. The results are promising enough to justify further study of this approach that requires few additional resources.

A relatively small study reports a positive effect of a Telephone-Nursing Intervention, called TIPS. This intervention comprises weekly calls by psychiatric nurses, trained to help patients with problem solving, offering reminders and coping alternatives with regard to common medication adherence barriers [121]. Overall adherence rates during the 3 months of the study were 80 % in the intervention group, versus 60, 1 % in the control group, as measured in 3-monthly pill counts in an outpatient sample of 29 participants.

Spaniel et al. [122] tested an ITAREPS that uses a mobile phone-based telemedicine strategy to remotely monitor patients with schizophrenia on a weekly basis to identify prodromal symptoms of relapse, enable early intervention, and reduce hospitalizations. ITAREPS produced a statistically significant 60 % decrease in hospitalizations over a mean of 9 months compared with the same period before entry in the program. Variables influencing number of hospitalizations after entry in ITAREPS were adherence to medication and the involvement of a family member.

Performance on a novel, virtual reality assessment of medication management skills, the VRAMMA, was investigated in 25 patients with schizophrenia and 18 matched healthy controls [123]. The VRAMMA is a virtual 4-room apartment consisting of a living room with an interactive clock and TV, a bedroom, a kitchen, and a bathroom with an interactive medicine cabinet. After an exploratory phase, participants were given a mock prescription regimen to be taken 15 min later from pill bottles located in the medicine cabinet in the bathroom of the virtual environment. Results revealed that (1) schizophrenic patients made significantly more quantitative errors in the number of pills taken, were less accurate at taking the

prescribed medications at the designated time, and checked the interactive clock less frequently than healthy controls; (2) in patients with schizophrenia, years of education and a measure of verbal learning and memory were linked to quantitative errors on the VRAMMA. This is the first study to provide evidence for the utility of VR technology in the assessment of instrumental role functioning in patients with schizophrenia.

The application of Schizophrenia Clinical Practice Guidelines in everyday health care are still described as unsatisfying. Within the project "Guideline-supported quality management in outpatient treatment", Janssen et al. [124] investigated whether guideline adherence and quality of outcome can be improved by implementing a computer-based, guideline-oriented decision-support system. Therefore, a disease-specific decision-support system was developed interactively presenting guidelines to support the physicians' decision-making process during the treatment of schizophrenic patients. It has been observed a strong initial but time-limited improvement with respect to the core aspects of outpatient treatment in schizophrenia in the experimental group. The findings suggest that decision-support systems can be used to enhance treatment outcome, medication compliance, and appointment adherence in schizophrenia outpatient care.

Community Interventions

Different models of community-based care have been developed to meet the diverse needs of patients with severe mental disorders. The key components of such interventions are the provision of a strong and supportive social network, close monitoring of clinical status including the medication regimen, provision of stable housing, and other supportive services [125]. Zygmunt et al. [25] noted that some community studies reported significantly greater medication adherence, although few of the studies included a rigorous assessment of such adherence.

ACT [125] and CM [126] were developed in the 1970s in response to closing of psychiatric hospitals.

ACT is an approach to provide services to patients with very severe mental illness who have difficulty accessing mental health-center-based services on their own. ACT offers an approach to integrated delivery of clinical services to patients with schizophrenia using a multidisciplinary approach, high frequency of patient contact, low patient-to-staff ratios, and outreach to patients in the community [2]. Supervision of medication follow through and close monitoring of symptoms are common activities of ACT teams. ACT, compared to routine care, has been found to significantly reduce hospitalizations and improve housing stability [127–129]. Although ACT appears to be an effective method of treatment delivery, the critical components which contribute to its benefits have not been precisely defined [25, 130].

Stein and Test [131] described a conceptual model of community treatment that encompasses six areas. These are material resources, coping skills to meet the demands of community life, motivation to persevere and remain involved with

life, freedom from pathologically dependent relationships, support and education of community members who are involved with patients, and a support system that assertively helps patients with the previous requirements. They describe implementation of this programme, which they entitled 'Training in Community Living', and compared this with short-term hospitalization plus after care. At 8- and 12-month follow-up, adherence with antipsychotic medication in the experimental group was significantly improved compared with the control group. Following the intervention, when patients returned to traditional community programmes, these benefits were lost.

Ford et al. [132] compared intensive CM with standard CM and also showed improvement in medication adherence at 18 months.

However, other studies of enhanced care management versus standard care failed to show improvement. For example Bond et al. [133] compared ACT with standard CM and at 6 months there was no difference in adherence between the groups. Similarly, Solomon and Draine [134] compared intensive consumer CM with intensive CM and showed no difference in medication adherence between the two groups at 2 years.

Dixon et al. [135] noted that despite the uneven quality of research into the effects of community care programs on medication adherence, many programs closely monitor patients with a history of nonadherence and consider regular medication use as an important treatment goal. It is suggested that the reduction in hospitalization associated with such models of care may in part be a consequence of improved medication adherence.

About the adherence in Supported Housing Projects, a cross-sectional naturalistic survey of adults with schizophrenia living in supportive housing facilities in New York City by Grunebaum et al. [107], showed that direct supervision of medication was associated with better adherence. The main finding was that medication supervision was related to the duration of medication nonadherence. The data suggested that medication supervision is more important than medication type or regimen complexity in determining medication adherence within residential facilities. Previous studies have shown that supervision of medication by family members or friends is associated with better adherence [98] but persons living in supportive housing are often without significant others to supervise their treatment. The results of this pilot study suggest that residential staff could take over this function and improve adherence by supervising medication administration.

An Expert Consensus Guidelines on the Treatment of Schizophrenia (1999) recommended programmatic interventions (e.g., ACT, partial hospitalization, rehabilitation services), especially for severely impaired and unstable patients [136].

In a 2000 Cochrane review on these interventions, Marshall and Lockwood [125] reported that patients in ACT were more likely to stay in contact with services, were less likely to be hospitalized, and were more satisfied with care than those in standard community care; however, they found CM to be of questionable value and doubted it should be offered by community psychiatric services [125, 126]. It is noteworthy that service-based interventions implicitly target the issue of engaging the patient with their key worker or developing a strong link to a support service such as day care or

supported housing. Having established a working alliance, many of the other interventions used in these programs incorporate problem-solving and behavioral strategies noted to be useful in promoting adherence in the primary outcome studies. Therefore, it is not surprising that about 50 % of studies of service-based approaches to the care and treatment of severe mental disorders also report a significant improvement in medication adherence [25].

Case managers or other members of the patient's treatment team (e.g., nurses) can play a valuable role in helping patients follow through on overcoming barriers to taking medication [137]. Many patients are capable of learning how to organize their medications with pill boxes, but require considerable practice before they are able to safely do it on their own. A case manager can demonstrate, observe the patient, and guide him or her toward competence at this skill. Some patients may not be capable of learning how to organize their medications on their own, but can take them safely as directed once they have been organized for them by the case manager. Behavioral tailoring to natural prompts such as brushing one's teeth is often most effectively implemented when a case manager can make one or two home visits. A home visit provides valuable information about the environment in which the patient lives, having the advantage of cueing the case manager about possible obstacles to implementing the behavioral tailoring plan.

Two studies in the last decade focused specifically on training of psychiatric nurses. In a randomized controlled cluster trial, Gray et al. [138] examined a medication management training package for Community Mental Health Nurses. Half of the 52 participating nurses received the training package, consisting of side effects management as well as training in effective treatment strategies for schizophrenia. The other half of the group of nurses received no training and delivered treatment as usual. At the 12-month follow-up, 29 patients treated by the trained nurses improved significantly in adherence rates on a clinician rating scale and on patient attitudes toward medication, as well as on symptomatology, compared with a group of 24 patients receiving care from the nontrained nurses.

In a comparable study [139] six US Department of Veteran Affairs medical centers (total participants 349) received basic guideline implementation strategies for the treatment of schizophrenia. Three of the six medical centers received an enhanced implementation strategy, in which physicians were trained to prescribe guideline-concordant. In addition, a research nurse identified barriers of adherence in patients: the nurses were trained in a protocol designed to assess medication adherence, strategies to maintain contact with the patients and provide feedback to the physician about adherence (barriers) and treatment preferences. Patients who received an enhanced guideline implementation strategy, in which a research nurse worked with them to identify and develop patient-specific strategies to overcome barriers to medication adherence, were almost twice as likely to be adherent at follow-up after 6 months. These data suggest that a patient-centered strategy to identify and overcome barriers to adherence can improve adherence to antipsychotic medications.

Psychosocial Interventions Additional to Pharmacological Treatments

Guidelines for the treatment of schizophrenia recommend the combination of pharmacologic and psychosocial interventions [2]. However, there is a lack of data on the utilization and effects of psychosocial interventions additional to neuroleptic treatment in routine care of schizophrenic patients. Linden et al. [140] investigated in 1711 schizophrenic outpatients the effectiveness of an antipsychotic treatment alone or in combination to a psychoeducation treatment. Psychosocial interventions were reported in 30 % of all patients. After 6 months of treatment with olanzapine, patients improved significantly in respect to their schizophrenic symptoms, psychosocial functioning, and quality of life. Patients receiving additional psychoeducation showed a higher degree of improvement than the other patients. They were more ill at the beginning of the study, but less ill at the end. Patients receiving psychoeducation showed also a trend to better medication compliance. The somewhat better adherence rate in psychoeducation patients (2.07 % vs. 4.60 % drop outs) raises the question of whether an optimization of drug treatment may improve the patient's health status. In fact, the data suggest that treatment outcome can become even better, if drug treatment is combined with psychoeducation.

Guo et al. [141] evaluated the effectiveness of antipsychotic medication alone versus combined with psychosocial intervention on outcomes of early-stage schizophrenia. Patients were randomly assigned to receive antipsychotic medication treatment alone or antipsychotic medication plus 12 months of psychosocial intervention consisting of psychoeducation, family intervention, skills training, and cognitive behavior therapy administered during 48 group sessions. 1268 patients completed the baseline assessment; 633 were assigned to receive antipsychotics combined with psychosocial intervention and 635 to receive antipsychotics alone. Overall, 744 patients (60.0 %) completed the 1-year follow-up: 406 (67.2 %) in the combined intervention group and 338 (53.2 %) in the antipsychotics-alone group. The rates of treatment discontinuation or change due to any cause were 32.8 % in the combined treatment group and 46.8 % in the medication alone group. Comparisons with medication treatment alone showed lower risk of any cause discontinuation with combined treatment ($P < 0.001$) and lower risk of relapse with combined treatment ($P < 0.001$). Nonadherence was noted in 2.8 % of patients in the combined treatment group and 5.7 % of patients in the medication alone group; rates of these events were lower among patients assigned to combined treatment ($P = 0.006$). Compared with those receiving medication only, patients with early-stage schizophrenia receiving medication and psychosocial intervention have a lower rate of treatment discontinuation, a lower risk of relapse and hospital admission.

More Frequent and/or Longer Visits may help foster an improved therapeutic alliance [3, 8, 10, 13, 142]. Frequent and personal meetings with detailed diagnostic explanations and positive outcome possibilities will help develop a

productive relationship between patients and physicians. Misdrahi et al. [142] reported that most effective therapies involve an interactional component between patients and care providers/therapists: a weak therapeutic alliance is associated with poor adherence in patients with schizophrenia who were hospitalized. Specific psychoeducational programs to improve therapeutic alliance should be implemented to achieve better therapeutic adherence and outcome alliance.

The experts stressed the importance of improving the therapeutic alliance and involving family members alliance [10, 23]. Research supports the importance of a partnership between patient and clinician and shared decision-making when treating patients with antipsychotic medications in order to improve outcomes and increase patient satisfaction and willingness to adhere to treatment [143–145]. Within the alliance, the patient and physician can work together to identify the optimal medication.

Symptom/Side Effect Monitoring is important because lack of response and side effect emergence can lead to poor adherence and discontinuation of medication against medical advice [94, 146]. It is important for clinicians to monitor symptom response on an ongoing basis (e.g., using a daily checklist) and be alert for adherence problems in patients who do not achieve an adequate response. Tacchi and Scott [23] reported that giving detailed information on how to manage specific side effects should they occur can increase the likelihood of sustained adherence.

Multifaceted/Mixed-Modality Interventions

Because adherence problems tend to be related to multiple factors, researchers often recommend multifaceted interventions. Multimodal approaches, by definition, recognize that educational, behavioral, and affective strategies are likely to improve adherence [2, 3, 10, 17]. It appears that individuaI, group and family work can all be undertaken using multimodal approaches.

Kelly and Scott [147] describe a study of 418 patients with schizophrenia or other psychotic disorders. Patients were assigned to one of three intervention groups or to a control group receiving standard treatment alone. The first intervention group received a series of up to three home visits focused on assessing the patient's current level of adherence, devising an appropriate behavioral approach for improving it, and encouraging a positive and supportive environment. The core of the intervention was the development of an individuaI "compliance plan". The second intervention—a clinic visit—was aimed at improving patient-provider communication designed to teach the patient to become an active health care consumer. The third active intervention was both the clinic and the home visits. 273 patients (65 %) completed follow-up at 6 months and ratings at this point demonstrated that adherence was significantly improved among the experimental groups compared with the control group. Continuous levels of adherence with medication at baseline and at 6 months between active treatments and the control treatment were significantly different. The results show that brief interventions can

significantly improve medication adherence in patients with chronic psychiatric disorders.

Hogarty et al. [148] undertook a 2-year follow-up of patients from high EE environments who had been randomly assigned to one of four treatment cells: (1) family psychoeducation; (2) social skills training; (3) both 1 and 2; or (4) supportive therapy plus medication. It was found that medication nonadherence was reduced significantly in the experimental conditions (rate = 21 %) compared with the control group (rate = 40 %).

Guimon et al. [149] studied a patient-and-family approach that involved group discussion of medication attitudes and behaviors. During group sessions patients discussed their conflicts about taking medications while a therapist and other group members provided suggestions about how to address these conflicts. Family members participated in similar groups. The intervention group showed superior medication adherence compared with standard care at 3- and 12-month follow-up.

Another study [150] included 39 such patients who were receiving case management services from a community mental health center. Patients were matched and randomly assigned to receive in a single session either (1) information regarding medication and its benefits, (2) guidelines for assuring adherence which encompassed all phases related to pill-taking including filling prescriptions, use of a pill container and self-reminders, or (3) the same guidelines as (2) but given in the presence of a family member who was enlisted in support. The results showed that adherence increased to about 94 % after the guidelines were given for both the individual and family procedure, whereas adherence remained unchanged at 73 % after the medication information procedure.

Dolder et al. [8] reviewed studies of 23 educational, behavioral, affective, or combination approaches to improve adherence in schizophrenia, 15 of which produced moderate improvements in adherence. The greatest improvement was seen with combination strategies. Reduced relapse, hospitalization, psychopathology and improved social function, gains in medication knowledge, and improved insight into need for treatment were also found. Longer interventions and a good therapeutic alliance were also important for successful outcomes.

The Danish OPUS trial [151], a large randomized clinical trial for first episode psychosis patients, investigated an integrated treatment, encompassing ACT, family involvement and social skills training and compared it to TAU. Adherence was only indirectly measured by participation in the treatment program, which showed significant differences after a follow-up of 1 year. Discontinuation of treatment for more than a month occurred in 8 % of patients in the intervention group, against 22 % in the control group. The percentage of patients stopping treatment in spite of necessity was 3 % versus 15 % in the control group, and the figure of patients making no outpatient visit was 4 % versus 15 %. At a 2-year follow-up, these differences were smaller and no longer significant for the groups stopping treatment or those discontinuing treatment for more than a month.

Masand and Narasimhan [152] recommended the following strategies to improve adherence in schizophrenia: optimizing antipsychotic therapy, minimizing adverse events, encouraging participation in psychoeducational programs,

treating substance abuse, involving family members, and fostering good therapeutic relationships.

Valencia et al. [153] reported that a strategy that included psychosocial skills training, family therapy, and antipsychotic medication improved symptomatology, psychosocial, and global functioning; reduced relapse, rehospitalization, and dropout rates; and increased adherence compared with treatment as usual after 1 year in outpatients with chronic schizophrenia.

Morken et al. [154] examined the effects on medication adherence of 2 years of integrated treatment in 50 patients with schizophrenia. Adherence to medication was examined in a randomized controlled trial of 2 years of integrated treatment versus standard treatment. The patients were clinically stable and had less than 2 years' duration of illness. Integrated treatment consisted of ACT, family psychoeducation and involvement, social skills training, and individual cognitive behavioral therapy. Good adherence was defined as less than 1 month without medication. Outcomes were compared over 12-month and 24-month follow-up periods. No difference in adherence between the integrated treatment group and the standard treatment group ($X^2 = 0.06$, NS) was found.

Summary of Main Results and Evidences

In a 2008 Cochrane review, Haynes et al. [155] have revisited the results of RCTs of interventions to help patients follow prescriptions for medications for medical problems, including mental disorders (but not addictions). Authors concluded that improving short-term adherence is relatively successful with a variety of simple interventions. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized. High priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders.

Early reviews [8, 25] covering interventions to improve adherence to antipsychotic medication lead to the following conclusions:

- Psychoeducational interventions show little effect on adherence, unless they are accompanied by behavioral and cognitive interventions that aim directly at medication attitudes and adherence behavior.
- Interventions specifically designed to improve adherence are more successful than programs intended to address a wider range of clinical problems, which suggests that a more intensive and focused approach is required to improve adherence rates.
- Combined and integrated interventions such as cognitive behavioral techniques, family interventions and community-based interventions are associated with favorable outcomes.
- More prolonged interventions or the use of booster sessions to reinforce and consolidate gains made during short term should be required.

In more recent reviews [3, 9, 10, 17, 23, 27], interventions that offered frequent sessions during a longer period of time, and especially those with a continuous focus on adherence, seem more likely to be successful, as well as pragmatic interventions that focus on attention and memory problems. The use of problem-solving interventions accompanied by technical aids is clearly promising. In recent years, attention was given to compensation for cognitive deficits in patients with schizophrenia, using environmental supports such as checklists, signs and electronic cueing devices. Some studies such as telephone intervention by nurses and especially CAT did show promising results, as well as a Pharmacy-Based Intervention. This suggests that all patients with chronic conditions and poor adherence could benefit from reducing access barriers with the use of Pharmacy-Based Interventions and concrete problem-solving interventions accompanied by technical aids. Possibly due to the prolonged duration of interventions, family interventions have shown positive results. Results by mixed-modality interventions suggest that a wider range of targets may be needed to promote adherence to medication, such as resuming rewarding life roles and regaining functional capacities. The positive effects of adapted forms of motivational interviewing found in earlier studies, such as CT or AT, have not been fully confirmed. Based on their comprehensive review of the literature, Julius et al. [9] recommended the following strategies for addressing adherence problems in patients with psychiatric illness: focus on strengthening the therapeutic alliance, devote time in treatment specifically to address medication adherence, assess patients' motivation to take prescribed medication, and identify and assess potential barriers to treatment adherence.

Conclusions and Future Directions

As with pharmacologic interventions with antipsychotics, matching behavioral interventions to increase adherence with pharmacotherapy to the needs of specific patients is desirable. Different factors affecting adherence require different interventions by the clinician. For example, if a patient has an unfavorable attitude toward taking or staying on medication, it is important to: routinely assess adherence; emphasize the therapeutic alliance; use a patient-centered approach, starting with the patient's point of view; stay symptom-focused rather than rely on the disease-model of interaction. Specific interventions include: CBT to emphasize working on problems as identified by the patient rather than the clinician; motivational interviewing to help facilitate motivation for positive change; family intervention to help educate and motivate family members in encouraging ongoing medication adherence. It is also important to appreciate the potential role of persistent symptoms as barriers to adherence and to address them not only with pharmacotherapy but also with effective behavioral interventions. Likewise, many patients have environmental barriers to adherence and interventions such as CAT may be helpful in addressing these barriers, together with good CM.

In a recent study Beck et al. [156] pointed out the importance of patients' individual perspective and experience with treatment. The authors reported that interventions to enhance medication adherence may be more effective if they focus on treatment related attitudes rather than on global insight into illness. Clinicians may not only enhance the patients' perceived necessity of antipsychotic treatment but also explore and address the patients' concerns and distrust in pharmacotherapy in a more personalized way. Modification of attitudes toward pharmacotherapy in general may serve as an indirect way of enhancing medication adherence [156].

Findings of another study [157] suggest that professionals, carers, and patients do not have a shared understanding of which factors are important in patients' medication adherence behavior. Professionals need to be aware of patients' considerations concerning their antipsychotic medication, in particular positive aspects of medication use, in order to provide effective support and guidance. Therefore, reducing the gap between patients' and professionals' views on the importance of medication-related aspects seems crucial. The discrepancies between patients' and professionals' views on the relevance of clusters should be further explored in future research.

Rüsch et al. [158] reported that implicit attitudes toward psychiatric medication predict, independently of explicit attitudes and diagnosis, key outcome variables such as perceived need for treatment. Self-reported adherence to the currently prescribed medication, on the other hand, may be associated more with explicit than with implicit attitudes and systematically tends to overestimate adherence. Implicit measures can tap attitudes toward psychiatric medication that participants are either unwilling or unable to report explicitly. These results suggest that the measurement of implicit attitudes toward psychiatric medication is feasible and may provide important information beyond explicit, self-reported attitudes as assessed by commonly used questionnaires or interviews. Future research should investigate how implicit attitudes toward psychiatric medications may change in response to interventions designed to improve treatment adherence [158].

Nonadherence remains a challenging problem in schizophrenia. There is a great demand for more studies on this multifaceted issue, especially considering the methodological problems that researchers face when measuring the effectiveness of adherence interventions, given the heterogeneity of the population treated and the large number of possible influencing factors. This calls for large well-powered studies targeting specific interventions.

Because adherence problems in patients with schizophrenia are likely to be complex and multi-determined, the use of strategies targeted at specific types of adherence problems might be more appropriate, thereby developing an individually tailored approach to promote adherence. This appears to be a promising direction, which will require regular updates and input of ongoing initiatives to determine the relevance of targeted interventions for specific problems and for certain subgroups of patients.

More evidence and evaluation of the validity and effectiveness of specific interventions aimed at improving adherence is required to further raise the standard of care and clinical outcome of patients with schizophrenia.

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Psychological Issues in Improving Adherence and Alliance

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The Patient–Doctor Relationship as a Determinant of Adherence to Treatment

From an intersubjective point of view, adherence to treatment can be defined as a multi-dimensional phenomenon [1] which occurs through the dynamic interaction of different variables which pertain both to the doctor (e.g., diagnosis, choice of medicines, prescription, therapeutic project, and goals of treatment) and to the patient (e.g., insight, attachment style, attitude toward the therapy, subjective well-being, and presence of a caregivers) (Fig. 1). All these factors, which are part of the therapeutic field built upon the relationship between doctor and patient, influence the therapeutic alliance. The phenomenon is multidimensional and this implies the necessity of taking into exam the greatest number of positive and negative factors involved. In psychiatry adherence represents one of the major current problems in the course of treatment. In fact, recent studies have shown that non adherence represents one of the most difficult issues in the treatment of schizophrenia [2] especially, and that a weak therapeutic alliance and low insight correlate with poor adherence [3]. The consequences of this phenomenon are quite obvious (e.g., scarce clinical improvement, chronicity, and relapses) and there are different factors which influence this.

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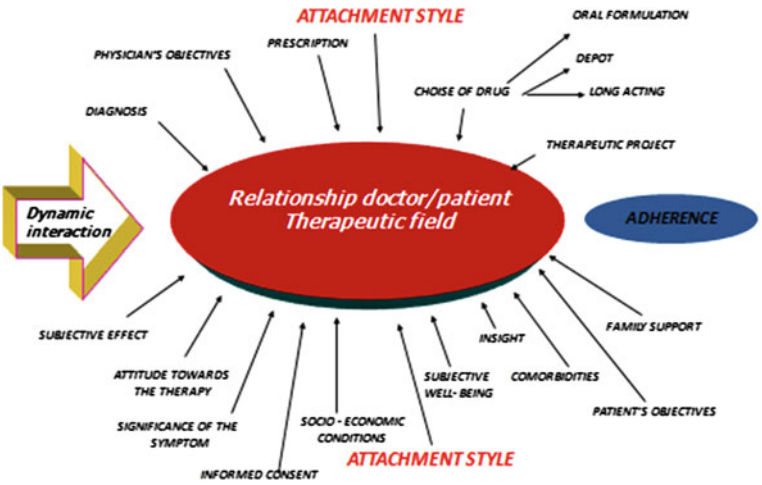

Fig. 1 Adherence: a multi-dimensional phenomenon (Niolu, Siracusano, 2005)

From Compliance to Adherence to the Alliance: Historical Notes

The concept of adherence is contiguous to that of compliance: compliance is defined as. "an amicable or serene agreement" and rather antithetical, as, "the act of giving in to pressure, demand, coercion... so servile.. accordance to satisfy formal requirements… promoted by official or legal authority". The adherence is defined as, "the act of forming a stable and trusting attachment (for a party, principle, cause)" [4].

From a semantic point of view, the two terms emphasize the fact that the subject is placed in a different position in relation to the agreement. The compliance presupposes the liabilities and the coercive characteristic of the action, induced by a hierarchically superordinate authority; however, adherence always seems to catch a glimpse of the assignment as a superordinate entity, but not experienced as coercive.

In the medical field these terms, in the course of time, have evolved from the point of view of the meaning and, consequently, also in the characteristics of their use: Sackett in 1976 defined the compliance as "the degree of coincidence of the behavior of a subject with the prescription" [5]; in 1986 Babiker spoke of "complex phenomenon that represents the subject's personal contribution to the management of their disease" [6]; Blackwell in 2000 speaks of "the degree to which the patient follows the doctor's prescription". In 1996, Hatcher, for the first time, combines the concept of *compliance* to that of the *therapeutic alliance*, calling it "a collaboration in which contribute, with varying degrees of activity, both the physician and the patient in an intersubjective dialogue", introducing the concept of *partnership* [7].

In 1991 [8], Probstfield used, for the first time, the terms *adherence* and *non-adherence* to refer to a therapeutic relationship in which the emphasis is shifted to the participation of the patient in the therapeutic choices. Focusing on the patient, the indexes of *subjective perceptions* and *patient satisfaction* are gaining greater value in the assessment of response to therapy and participation in treatment.

Subjective perceptions and patient satisfaction are elements that must be distinguished from the more general assessment of the drug's *effectiveness* on symptoms and the *side effects* objectively demonstrated. To confirm this observation there is the fact that, with the same effectiveness and incidence of side effects, many interruptions of treatment are to be related to low scores in ranges of *subjective well-being* and patient satisfaction [9]. A significant step forward was made with the introduction of informed consent, which is an instrument through which the patient expresses his desire to join the therapeutic program.

Within the informed consent, the terms adhesion and adherence must a fortiori be distinguished. The adhesion is, as has been said, a general acceptance a priori of the treatment proposed, before it has started, while *adherence* refers to a contract in which patients, after having experienced the effects of the treatment, express their intention to continue it.

Through the expression of informed consent, the evaluation of *subjective perceptions* of patients and the expression of their *satisfaction* for the ongoing treatment, it establishes a *negotiation* and *dialogue* between *informed patient* and *caregiver*, that is the person who takes care of the patient (e.g., relative, assistant, medical-nursing staff).: This involves the active involvement of the subject in establishing treatment goals, and therefore, the establishment of a *therapeutic alliance* (see Table 1).

The interaction is called dynamic because each of the factors listed may vary over time within the therapeutic relationship. Examples of this include the introduction of a new drug, suspension and/or reduction of the previous treatment, the decision to start psychotherapy in the course of a drug in a psychological relationship.

Table 1 Niolu e Siracusano, 2005

Period	Type of relationship	Role of Doctor/Patient
Early twentieth century	Hierarchical relationship	Doctor: role of taxation Patient: passive role
Fifties	Hierarchical relationship	Doctor: paternalistic role Patient: passive role
Nineties	Collaborative relationship	Intersubjective dialogue
Two thousand years	Shared decision making model	Therapeutic choice shared

Subjective Well-Being

Satisfaction and well-being are subjective experiences: the way patients experience drugs and sensations that patients experience when taking psychopharmacological therapy appears to be an essential clinical data for both the overall understanding of the patient's attitude towards therapy and for predicting the adherence to treatment [10]. In addition to the factors previously considered, these feelings have a significant impact in maintaining adherence. The patient's attitude towards the drug by psychopathological conditions, clinical severity of the subject and the side effects.

As neuroleptics were introduced into clinical practice, patients, in the position of influencing the selection of therapy, have now spoken of the "unpleasantness". The side effects that mostey affect adherence in a negative way are: extrapyramidal symptoms (akathisia in particular), weight gain, sexual dysfunction and, more generally, the negative sensations related to the treatment [11–14]. In fact, despite the side effects of drugs are a cause of discontinuation of therapy, response and subjective well-being to treatment with antipsychotics are the most important predictors for adherence [12, 13, 15].

In this regard, it is useful to remember that the line between side effects and subjective effect is very thin, and is difficult to detect in the patient's report; however, it is important that in the clinical interview is thoroughly investigated, because frequently, patients tolerate serious side effects well if they do not identify their subjective feelings as particularly unpleasant. The subjective experience is often found in the patient's idea of his or her illness and what is the idea of recovery or, more simply, to "be better". The most frequent unpleasant sensations reported by patients taking psychiatric drugs recall "feeling strange and drawn, without feelings, difficulty thinking" [12, 15]. In summary, it is believed that some unpleasant sensations that arise during treatment represent a specific element in its own right, usable in order to provide nonadherence, and then to implement strategies which limit the interruption of therapy. The clinical importance of the study of subjective responses lies, no doubt, in the ability to accurately predict sufficient adherence to treatment in patients with schizophrenia, as well as, according to Dworkin, to recognize subjective feelings to treatment as an indicator of initial symptomatic response [16]. The earliest evidence dates back to the end of the 1990s; Singh and Smith in 1973 reported that patients with dysphoria during treatment with haloperidol had a negative outcome over time [17]. More recent studies have confirmed that the occurrence of negative feelings after 24 to 48 hours of treatment with neuroleptics significantly correlated with poor adherence within 3 weeks or less in response to treatment [12]. Another study conducted on a fairly large sample of patients (150 subjects) with a diagnosis of chronic schizophrenia showed that slightly more than half of the participants did not follow the therapy. Among them, the patients did not differ by sex, age, and total time of hospitalization, but a significant negative correlation was observed between subjective experiences (assessed with the Drug Attitude Inventory-DAI) and poor adherence;

also almost all patients (80 %) within the sample had a *pattern* of adherence in accordance with the type of subjective response reported [12]. Recently, other experiences have allowed us to observe that the attitude and feelings of the patient toward medication, assessed with specific scales such as the *Drug Attitude Inventory* (DAI), *Subjective Well-Being under Neuroleptic Scale* (SWN), and *Rating of Medication Influences* (ROMI) are not explained by the overall severity of positive or negative symptoms: not necessarily in sicker patients observed an approach to the treatment worse than those with milder symptoms and it always show that the feelings related to the treatment and the way in which the subject experiences the relationship with the drug are something autonomous, not closely related neither to the state of the disease nor to side effects. This data is very important and should be constantly kept in mind: an improvement of psychopathological picture, in fact, is not always associated with a similar improvement in subjective well-being, or to a greater adherence to therapy by patients.

The relationship between doctor and patient, fundamental in all branches of medicine, is in psychiatry, the *core* of the therapeutic program and ensures the therapeutic continuity. The therapeutic relationship between doctor and patient was found to be significant for adherence to treatment in all psychiatric conditions. The therapeutic relationship was investigated as it was emphasized by Freud. He wrote that, "The first aim of treatment consists of fixing [the patient] for the treatment and the person of the physician". A discontinuity in treatment does not merely indicate an interruption in the assumption of drugs, but represents an important signal that something in the doctor–patient relationship has changed or is changing. This relationship is peculiar, and as a matter of fact, even in a doctor-patient relationship that is primarily based on psychopharmacological prescription, the simple drug prescription has the value of "relational act" and necessarily involves the construction of a relationship that takes into account the drug use, giving to therapist and patient roles that turn around this central element. Therefore, in choosing a therapeutic program the primary target to be achieved (if the diagnosis is correct and the chosen drug effective) is to ensure the appropriate therapy intake, at the right doses and for the prescribed time, which in turn, affects response, remission, relapse, recurrence and the possible development of resistance and / or chronicity, which will shape the course of the disorder. In fact, neither the accuracy of diagnosis, nor the right medication can provide sufficient guarantees about therapeutic adherence. The ability to predict, within certain limits, adherence to treatment can occur only if the physician has a thorough knowledge of his/her patient: he/she must have much information about his/her previous history, personality traits, capacity of insight, his attitude toward drugs in general, and psychiatric ones in particular, his illness idea: the nature of it and the extent to which it has changed his life, what he means by his idea of getting better, the family and social network, how they establish and maintain, if this happens, significant emotional ties (attachment style). To pursue this objective, the *interview* is the spatial, temporal, and mental location, to collect all the elements and to lay the foundations for the creation of a therapeutic field. As mentioned above, in psychiatry any type of doctor–patient counseling, and in particular the first

interview, is already a relational and therapeutic act. In order to achieve this objective, *the interview* represents the spatial, temporal, and mental place to collect all of the elements in play and to lay the foundation for the creation of a therapeutic field.

As mentioned above, in psychiatry any type of doctor–patient meeting, even and especially the first interview, is already an act and relational therapy.

The points on which the therapist must focus during the first interview are:

- Active listening (processing of biological, psychological, and motivational meaning of the symptoms, "mapping" of the patient)
- Setting up a dialogue and a therapeutic relationship based on clarity in some areas:
  - on his own idea about drugs,
  - on the idea of the patient about medication and its previous experiences,
  - on the manner of *prescription*,
  - on the reasons for choice of the drug,
  - on the outcome expectations,
  - on the expectations of side effects;
  - on the involvement of the patient and underscoring his or her role in monitoring and reporting therapeutic and side effects, and;
  - on the involvement of the family network in the construction of the covenant: evaluation of the real possibility of taking the prescribed treatment, detection and prompt reporting of symptoms "sentinel" of relapse and practical help in taking the drug daily.

The follow-up interviews are meant to the monitoring of drug treatment and to strengthen the collaborative approach established in the first interview, through the following steps:

- the verification of the patient's reactions to the drug prescribed;
- the verification of the difficulties encountered in following the prescription;
- emphasizing the importance of the point of view of the patient, his subjective perception;
- the verification of the degree of adherence as compared to the predictions made in the first interview;
- evaluating the efficacy and tolerability of treatment (side effects);
- dosage adjustment, and
- feedback from the family.

The *prescription* is at the same time the official start of drug therapy and the endpoint of a path that has developed through the execution of all previous diagnostic and therapeutic acts, from which now, largely depends on the outcome of the prescription. The context where the prescription happens is a relationship between doctor and patient which is human and dynamic and goes beyond the symptoms to shape the "therapeutic field", an area of intersubjectivity, which is the result of this dynamic interaction between factors that belong to the patient and the therapist, and influence, in various measure, the achievement of an adequate therapeutic alliance. This latest is defined as the relational base on which a therapeutic project is built, a relationship of trust and cooperation with mutual sharing

of skills, objectives, and methods, that has a crucial effect on adherence to pharmacological or psychotherapeutic treatment, issues which areas fundamental as they are problematic for all medicine and for psychiatry in particular.

Alliance and Psychodynamic Issues

The therapeutic alliance is also defined as a relationship to which both doctor and patient contribute, with varying degrees of activity. It is the relational collaboration established between the physician and the patient with the aim of building a relationship of trust and mutual cooperation. On this relational base, a treatment plan is built, and allows the patient and the physician to plan together the course of treatment articulated in the time and manner necessary to address the specific disorder.

There are two different types of therapeutic alliance. In the first type, called "*helping alliance*", the patient perceives the therapist as "warm, helpful and supportive", in this case it may run the risk of reducing the relationship in terms of "demand-response", whereby the patient "asks" and the doctor, colluding, "provides" the drug. In this case it is important to insist on engaging the patient in a reciprocal relationship, in which he must take the most active and proactive attitudes, even with respect to dose adjustments and decisions on drug. The second type of alliance, called "*working alliance*", is based on a sense of common work, that targets the containment of the discomfort that hinders the patient. Key points of this type of alliance are the sharing of similar interpretations of the etiology and for the reasons of hardship by the therapist and patient, combined with the feeling of a positive evolution in the ability of cooperation of the patient in the treatment program, through the acquisition of therapeutic tools borrowed from the progress of the relationship with the therapist.

It is possible to foresee a third type of alliance, which in successive stages, is found to shift from a *helping to a working* alliance during the gradual, but steady, development of the therapeutic relationship [8]. The "*intersubjective alliance*" [18, 19] is a new concept derived from psychotherapy, later adapted to the pharmacological therapeutic relationship. To develop an effective and appropriate patient–physician relationship, the psychiatrist must always be aware of working with a people who have their own personality, feelings, sensitivity and intelligence, apart from symptoms and illness. Psychoanalytic theories suggest that the quality of the therapeutic relationship is linked training to interpersonal relationship training of unconscious reactions such as transfert and controtransfert. Since the beginning of his studies, Freud had understood that the work of revelation, which is essential for the success of psychoanalysis, required a collaborative attitude and cooperation between patient and therapist. Placing inside the "irrepressible positive transfert" (conscious positive feelings toward the analyst, who helps the patient to overcome the resistance), Freud used the term "rapport" to refer to this important aspect of patient–therapist relationship and called it the

"vehicle for the success" [20]. Transfert is defined as the shift of thoughts, feelings, desires, and behaviors of the patient, originally facing significant characters of his childhood world, on the therapist. Through this shift, the patient turns the memories into present life: in the analysis space. However, the controtransfert is, however, the wide range of reactions that the doctor may have toward the ill. It may take the form of positive or negative feelings (e.g., a doctor who has feelings of anger, hostility, antipathy toward the patient, tends to assume a destructive and ineffective attitude in the relationship) [21]. According to Freud, the conditions for withdrawal of the setting (opacity, silence) create frustrating situations for pulses so that they win the obstacle of resistance, actualized in the analytic relationship. In contrast, in the cognitive model, the conditions of interpersonal security, offered by the therapeutic relationship, promote the awareness and development of autoriflessive more heuristics activities. The experience of a positive relationship with the therapist can change the negative forecasts of the patient's interpersonal patterns. Such corrective interpersonal experiences concern the affective and cognitive side and the disposition of the action. Looking at the therapist the patient can assimilate ways of acting more useful than those usually adopted. The therapeutic outcome is most significantly correlated with the therapeutic relationship rather than the different psychotherapeutic techniques [22].

In this complex model of prescription, focused on relationship, the attachment styles emerge as central points. As the therapist and the drug represent attachment figures and the patient is a caregiving figure, each of them enters the relationship with their Internal Working Models (IWM) and behavioral patterns, which must be taken into account in the construction of a prescription to optimize adherence. Attachment theory also contributes to the understanding of working alliance by providing a framework to conceptualize the way in which therapist and client factors interact in determining the quality of the relationships. There is empirical evidence to suggest that therapist attachment style is influential in the development of a therapeutic relationship [23].

The attachment system has its basis in the innate propensity of human beings to form strong emotional bonds with their figures of reference, which Bowlby calls "particular others" [24, 25]. The evolutionary purpose of the attachment system is to find a caregiving figure that the subject perceives as strong and reliable. This attachment system is established according to the different qualities of the mother-child relationship, resulting in several "attachment styles", with varying characteristics depending on different dynamic and circular patterns of demand (attachment) and answer (caregiving). Attachment style is the way in which each individual assumes the innate propensity to form affectionate bonds with others. The attachment developed within the infant-caregiver relationship is thought to form the "secure basis" of future relational dynamics.

Research by developmental psychologist Mary Ainsworth in the 1960s and 1970s, through the protocol of the Strange Situation, reinforced the basic concepts and introduced the concept of the "secure basis". As such, she developed a theory which included a number of attachment patterns in infants: secure attachment, insecure-anxious avoidant attachment and insecure-anxious ambivalent attachment.

Infants who are "securely attached" use their caregiver as a secure basis while exploring new surroundings; such infants seek contact with, and are comforted by, caregivers after separation. Infants described as "anxious-ambivalent" have difficulty using the caregiver as a secure base; these infants seek, then resist, contact with caregivers after separation. Finally, infants with an "avoidant attachment" style do not exhibit distress upon separation and do not seek contact after the caregiver's return.

In 1985 M. Main identified, along with the attachment styles delineated by Ainsworth, a fourth attachment style in children, that she called "disorganized" [26–29].

The "disorganized" style, evaluated as a risk factor for the onset of a series of psychological disorders, can be characterized by the absence of a coherent organized behavioral strategy, to cope with the stresses that the child receives during the Strange Situation. Mary Main, based on the Strange Situation for children, designed by Mary Ainsworth, created the Adult Attachment Interview (AAI), a semistructured interview assessing attachment style in adults. According to these measures adults have four attachment styles: secure, anxious–preoccupied, dismissive–avoidant, and fearful–avoidant. The secure attachment style in adults corresponds to the secure attachment style in children. The anxious–preoccupied attachment style in adults corresponds to the anxious–ambivalent attachment style in children. However, the dismissing–avoidant attachment style and the fearful–avoidant attachment style, which are distinct in adults, correspond to a single avoidant attachment style in children. Another pattern of adult attachment style is the one proposed by Bartholomew and Horowitz. These authors focused on a pattern of attachment related to Internal Working Models (IWM) of self and others. For IWM we refer to the mode in which subjects define themselves and others in terms of intimate relationships. Bartholomew and Horowitz delineated four different patterns of attachment (see Table 2) and developed the Relationship Questionnaire (RQ) [30], which highlights the subjective perception of the interpersonal relationship relative to each of the attachment styles. Integrating data regarding attachment in adults with data on the different meaning of emotions of attachment in mother/ child relationships [28, 31, 32], we strived to extrapolate

Table 2 Attachment styles and internal working models IWM[a]. Copyright © 1991 by the American psychological association. Reproduced with permission [30]

	I.W.M.of other Positive	I.W.M.of other Negative
I.W.M.of self Positive	Secure	Avoidant/Dismissng
I.W.M.of self Negative	Anxious/Preoccupied	Avoidant/Fearful

[a] Internal working model: Modality with which subjects define themselves and others on the basis of interpersonal relationships

hypotheses about the role of attachment style in the doctor-patient relationship and adherence to treatment. In the fearful and preoccupied attachment styles, ambivalent emotions of attachment itself prevail, assessment of ambivalent emotions of attachment itself, while in others, the person would doubt the effectiveness of these emotions by evoking a coherent response. Individuals with preoccupied attachment styles would have more positive beliefs about help-seeking, but may still be relatively ineffective in regulating distress through seeking support or methods of self-regulation. This is reflected in the therapeutic relationship where adherence sometimes is inconsistent, sometimes exaggerated, and sporadic. In avoidant attachment, emotions are classified by subjects as a source of irritation moreover as a sign of personal inadequacy for themselves. It should be obvious that the identification of the attachment style of the patient must be supported by an equally clear understanding of the therapist's own attachment style. This aspect, necessary in a psychotherapeutic relationship, must also be considered as fundamental in the psychopharmacological relationship, where the drug itself is an attachment figure [33]. Identifying the patient's attachment style can be useful to the physician to build a good therapeutic alliance and to predict adherence to treatment. With particular attention on case managers of patients suffering from severe and persistent mental health problems, *Dozier and colleagues* found that physicians with secure attachment style, assessed with the AAI, were less likely to develop a therapeutic alliance with patients with dismissing or preoccupied attachment style [34]. Instead, another study showed that patients with opposite attachment style compared to their doctor established a stronger therapeutic alliance [35].

Attachment style, therapeutic relationship, and adherence in schizophrenia

In schizophrenic patients with avoidant attachment style there is a greater tendency to develop positive symptoms and a lower adherence to pharmacological therapy that, in contrast, is higher in patients with anxious attachment. Individuals with avoidant attachment style will tend to show avoidance coping styles which are associated with poorer outcomes because they have negative expectations about help-seeking; in contrast, patients with preoccupied attachment style develop more positive lived experiences about help-seeking but may still be relatively ineffective in regulating distress through seeking support or methods of self-regulation [36]. In disorganized attachment style the emotions in the relationship are often multiple and dissociated, and then reflected in an interpersonal relationship of this type. The clearest example concerns the therapeutic relationship with patients with borderline personality disorder or dissociative disorder patients [28].

To date there is limited research investigating attachment theory relevance to psychosis. The starting point is the finding of high levels of insecure attachment in patients suffering from psychosis. Cognitive models of psychosis emphasize the importance of self and other schemata in the development and maintenance of psychosis and according to these theories, early life events, such as trauma related to the breakdown of meaningful interpersonal relationships, can lead to a vulnerability to perceive others as a threat and this could contribute to the development of psychotic symptoms in adulthood [37]. The attachment theory emphasizes the importance of interpersonal events and trauma in psychotic *social cognition* [38].

Particularly, this theory is fundamental to understanding specific symptoms associated with psychosis (e.g., voice hearing, paranoia, and negative symptoms). There are indications that specific types of insecure attachment predispose individuals to the development of different symptom profiles associated with psychosis or once developed be a key factor involved in their maintenance. In this regard, an example is the theory that distinguishes between the two types of paranoia: "poor me" paranoia, related to high self-esteem ("I'm persecuted because they envy me") and "bad me" paranoia, related to low self-esteem ("I'm persecuted because I'm guilty"). In terms of attachment style, the two types of paranoia can be related to the dismissing and fearful styles, associated with negative beliefs about others, but which differ in terms of self-view. Particularly, clinical studies show that there is a correlation between dismissing attachment and "poor me" paranoia and fearful attachment and "bad me" paranoia [39]. Research with nonclinical samples has supported this theory by finding an association between avoidant attachment style and negative schizotypy and anxious attachment style and experience of nonclinical paranoia and voices [40, 41]. A key factor in the outcome of psychosis is the quality of the therapeutic relationship and moreover, an important element is the attachment style of these patients. Several studies have shown that a key factor for the therapeutic treatment compliance is the development of a secure attachment style. Individuals diagnosed with schizophrenia and with a dismissing attachment style have a greater tendency to beware of the physician, a lower tendency to assume drugs and less self-disclosure; on the contrary patients with preoccupied attachment style show a greater tendency to require attention from the doctor, although they also have poor compliance [42]. In addition, the avoidant attachment style, is linked to a poorer adherence to treatment, while anxious attachment is associated with better therapeutic alliance [43]. Insecure attachment as a while leads to poor adherence to treatment and poor engagement in psychiatric services [44–46].

Individuals with psychosis of multiple constructs may potentially influence medication adherence or engagement in services: symptoms, insight, personality traits, alliance, childhood trauma, substance abuse, social functioning, and sociodemographics. More positive symptoms, having witnessed violence as a child and high agreeableness as a personality trait predict poor medication adherence; physical abuse as a child, lack of knowledge regarding consumer rights, difficulties in building an alliance, low neuroticism, high agreeableness predict poor service engagement [47]. Comorbid depressive symptoms may lead to less involvement in care services, and patients with insecure attachment style and greater severity of depressive symptoms show a lower adherence regardless of the presence or absence of psychotic symptoms. Patients with severe depressive symptoms and insecure attachment style may difficulties attending to regular services. Individuals with anxious attachment style, requiring external approval to increase their self-esteem, may refuse treatment if they feel that the staff is unable to respond immediately to their own needs and requests. Finally, patients with avoidant attachment style tend to deny the importance of close relationships and tend to not engage in important and helpful relationships [48].

Moreover, the attachment theory allows us to make assumptions about the way in which attachment style can be modified on the basis of the therapeutic relationship [49].

Toward the Concept of Concordance of the Therapeutic Project

The therapeutic intervention in schizophrenia is a complex procedure, which requires a variety of approaches. The pharmacological approach is still the mainstay of treatment in patients with schizophrenia. Despite the introduction of atypical antipsychotic with a good tolerability profile and with fewer side effects, the main problem of the treatment of schizophrenic patients is medication nonadherence. Therefore, strategies to improve adherence must be based on a multidisciplinary approach. The WHO stresses the importance of increasing interventions aimed at skipping the factors "related" to the patient. Strategies to improve adherence in patients are articulated through various levels, ranging from educational programs that include family, to cognitive behavioral psychotherapy. On the pharmacological point of view, one should choose the pharmaceutical medications according to the clinical characteristics and medical history of the patient, monitor the possible side effects, ensure that the patient understands the regimen and promote family and social support that encourages the regular intake.

Therefore, one should integrate psychosocial, pharmacological and planning interventions for an effective strategy to improve adherence [50, 51]. A good doctor–patient relationship is important in the construction of adherence, as it provides the patient with a framework in which he or she can handle needs and anxieties linked either to the pathology or to the treatment. Patients should feel free to show their doctors their concepts of illness and health, and to discuss and gather information on the effectiveness of therapies and possible side effects. Patients should, always, have the perception that the therapist is interested in them as people and not only from a medical–technical point of view [52].

Currently, the majority of psychotherapy research focuses on the attempt to bring together method and the relationship. There is greater emphasis on the emerging dynamic process rather than the therapeutic technique. The quality of the therapeutic relationship seems to be the main element of care, more than other techniques. The aim is to increase the therapeutic efficacy and the adherence to treatments. Dworkin use a "relational lense" [53] through which there is a focus on the real relationship, different from the phenomena of transference and countertransference, on the development and maintenance of collaborative working alliance, and empathic attunement with the patient. The Author specifically refers to the treatment for trauma spectrum disorder Eye Movement Desensitization and Reprocessing (EMDR) and speaks of "relational imperative": a working alliance that will allow therapist and patient not only to work side by side for the achievement of a goal (symptom) but also to be one (face-to-face) in a relationship. Authors from different theoretical settings refer to the same phenomenon

using different terminology and descriptions. A Boston group named "The Boston Change Process Study Group," in the wake of evolutionistic cognitive psychology, proposed some conceptual changes in the quality of interventions. They focused the concepts of implicit relational knowledge and on the idea that change happens in "meeting moments", through changes in "ways of staying with", meaning the change is given by the therapeutic relationship itself. In the therapeutic relationship something new is built that changes the intersubjective environment. The past experience is recontextualized in the present, so that the subject comes to act with a different mental landscape, which produces new behaviors and new experiences in the present and in the future. The implicit relational knowledge is, therefore, obtained through interactive and intersubjective processes, which alter the relational field in the context of the shared implicit relationship [54].

According to this approach, a meeting between therapist and patient is preceded by a set of "present moments" in which one moves subjectively to each other. When a present moment takes a strong affective valence, it becomes relevant in the therapeutic process, and is defined as "the moment now". In the event that it is recognized and accepted by both partners during the therapeutic relationship, it would lead to mutual harmony: a true moment of encounter and emotional understanding. The "moments of meeting" are the focal events that act within the "shared implicit relationship" and are able to change it by changing the implicit knowledge, both intrapsychic and interpersonal.

The key concepts of this change are the nature of dyadic adapting and directionality, sloppiness, and vitalizing of the therapeutic process. The therapeutic relationship is an ongoing process between therapist and patient, which directly creates a change and therefore a so-called dyadic process. The process connection is directional: searching and finding a direction leads to repetitions, errors, many attempts, and exploration. These movements are called sloppiness of directional flow. The vitalizing of the therapeutic process is given its own contribution to the adapted interactions. The mutual adjustment is the vitalizing. The quality of relationships depends on how the therapist or the patients advance forward and expand the shared therapeutic field. The quality can not be separated from the directionality of the process; it is given by the direction of research and adaptation, and by the attempts to expand the range of emotionally charged experiences that can be brought into the therapeutic relationship. To the extent that these processes are understood dyadic should emerge in the therapeutic relationship, a relationship of trust and mutual vitalizing. These dynamic processes when activated move in the direction of increasing integration, consistency, and smoothness in the patient's ability to make a balance in significant trade with others. The Boston group proposed a change in the classical psychoanalytic theory and also of current theory. Traditional psychoanalysis emphasizes the fact that the patient is contributing to the therapeutic relationship and the therapist is an "intervention" as if he were speaking from the outside. The current theory proposes a reconceptualization of the alliance as the "continuous process of intersubjective negotiation". For the Boston group, the core process in treatment is instead, trading the combined direction. The change of the dyadic state is unrelated to the emergence of the

"meeting point" between the two interacting subjects. Much of the environment comes from intersubjective implicit relational knowledge, which is reconstructed in the course of therapy. The process of change takes place during the re-enactment of the shared implicit relationship during "moments of meeting", thus opening new and fruitful perspectives for therapeutic change.

This emphasis on the intersubjective relationship is what is also proposed by the Value-Based Practice (VBP) also proposed, providing specific tools that allow us to carry out more patient-centered scientific work. VBP is the theory and skills for effective healthcare decision-making, where different (patient's and therapist's) are involved (and potentially conflicting). Good process in VBP, as shown, is based on 10 key indicators. The starting point for good process in VBP is the careful attention to the individual patient. Where the values are in conflict, however, the VBP seeks to achieve a balanced approach to clinical decision-making by drawing on a range of different perspectives of value, represented in this case by the multidisciplinary team. Achieving a balance of value perspectives in turn depends on four key clinical skills: raising awareness, reasoning skills, cognitive abilities and communication skills. Approaches based on values and those based on evidence, are complementary [55]. In particular, as David Sackett (one of the greatest exponents of the practice of the evidence) pointed out, they are both essential to create concrete collaboration between professionals, patients, and patients' families. This aspect of the smooth running of the VBP is reflected in the model of the Participatory Decision-Making System.

The therapist must be aware of his or her own values consider that these will enter into the relationship with his patient, and that he or she will face the patient's values. An "alliance in values" is one of the best pathways to therapeutic alliance and adherence to treatment.

Intersubjectivity is the central fulcrum on which converge the efforts of different psychotherapeutic approaches and therapy in a broad sense. Intersubjectivity is a tool for the consolidation of the therapeutic alliance that is not only aimed at achieving the therapeutic objective (psychotherapeutic, pharmacological or combined) but also at building a new relational model, which allows changes in the different modes of the patient is relational style. One of the most significant aspects of the relationship between attachment and intersubjectivity, referring to the ability to relate with each other, is the different role they occupy in the scale of human development, both as development of the species (evolution) and personal growth of each individual. These are marked by the overlapping of different more advanced systems, more and more advanced, which regulate the transition from the stage of exclusively biological evolution and development, common to other primates, to more specifically human, characterized by symbolic language. The upper level is represented evolutionarily by intersubjectivity, characterized by symbolic language, and the ability to build, through this, meanings shared by members of our species. The link between less advanced level of report/motivation and the latter is the ability to enter a peer relationship with each other through the ability of joint shared attention on the same object, such as happens in the social game and in affiliation to a group. According to recent studies, this ability to

"perceive the other human being as fundamentally similar to himself intentionality" begins to develop in children as early as the 9th month of life in all human cultures, so it should be considered as a further step in the Darwinian adaptation of Homo sapiens [56, 57]. This step is certainly crucial in marking the passage, the ability to relate to the child's personal identity through the fusion mechanisms of imitative gestures of a "similar" but perceived as "other."

So the transition to intersubjectivity as independence from the driver would be an exclusively "human" feature. All other behavior, as we have seen are determined by motives evolutionarily determined and aimed at survival. Intersubjectivity, according to most studies of evolutionary anthropology, would be independent for a very specific reason. The behaviors of affiliation and cooperation, also present in primates, however, are determined by the aim of strengthening the forces to achieve a goal, such as to escape a predator or to reach a prey [58]; therefore, they are always based on the interest of the individual, which is motivated to obtain a specific advantage in the report. In the intersubjective relation, mother–child exchanges are accompanied by expressions of "joy" that have no match with personal benefits that are unrelated to the exchange itself (reciprocity). The "purpose" of the exchange seems to be the exchange itself, namely the report, in the absence of more benefit to the individual [59].

Close to this is the concept of "intersubjective consciousness" [60–62], uniquely human, too. It is the ability to have a continuous dialogue with a foreign interlocutor internalized interlocutor: Intersubjectivity is like an ever running that does not need external stimuli (motivation) to be turned on, but that is always running as long as we are awake. It is important to note that this game system, governed by precise reasons partly innate and partly learned in relation to the environment, is mostly done initially using preverbal signals, implicit, characterized by different emotions. The emotion has an immediacy of impact on both individuals who come into contact, making it clear to both what is the meaning and motivation of the report, without conscious and rational reprocessing. Everything that happens in an intersubjective dimension is primarily mediated by emotion; the ability (or inability) to recognize and match the emotion of the other determines the quality of the relationship: secure, insecure, disorganized, and the subsequent ability of sharing with each other jointly ("joy of sharing"). Empathy is the key emotion of intersubjectivity.

In conclusion, adherence is a complex phenomenon and the drug's intake represents the culmination of a series of aware evaluations of and by the patient. Elements that appear to play significant role are many, but a good patient–physician relationship is essential for the development of therapeutic approaches that address the individual problems interfering with adherence. A positive influence on adherence is possible if professionals focus on positive aspects of drugs on a better insight and on the promotion of a positive therapeutic relationship with patients and their caregivers. A key role plays also played by the so-called subjective well-being, which is defined as the subjective sensations under neuroleptic treatment, to be distinguished from side effect of drugs and which assesses the physical and mental subjective feelings the patient experiences. These feelings having to do with body and mind image and sensations, very often lead

the patient to feel "altered" and "detached from self", and for this reason, much more than side effects lead to treatment discontinuation [63].

Another hot point is quality of life, as "functioning" is becoming more and more one of the most important key and ambitions goals of treatment. Finally, going back to our initial definition of adherence as a multi- dimensional issue, we could say that the concept of concordance of the therapeutic project overlaps with the concepts of doctor–patient relationship, therapeutic field and intersubjective alliance. Factors belonging to the physician, such as diagnosis, prescription, choice of drug, physician's objectives, attachment style, therapeutic project, meet with factors belonging to the patient and his caregivers, subjective effect, attitude toward the therapy, insight, attachment style, subjective well-being, socio economic conditions, informed consensus, significance, family support, patient's objective, in a dynamic therapeutic field represented by the doctor–patient relationship.

This meeting becomes concordance only when the physician succeeds in matching his face of the coin with the patient's one, for every single factor, through an intersubjective and dynamic balance which goes along with illness course but, moreover, with patient's lifespan and life events.

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