Schizophrenia Bulletin vol. 32 no. 4 pp. 724–742, 2006
doi:10.1093/schbul/sbj075
Advance Access publication on May 17, 2006

Defining and Assessing Adherence to Oral Antipsychotics: A Review of the Literature

Dawn I. Velligan[12], Yui-Wing Francis Lam[3], David C. Glahn[2], Jennifer A. Barrett[2], Natalie J. Maples[2], Larry Ereshefsky[4], and Alexander L. Miller[2]

[2]Department of Psychiatry, University of Texas Health Science Center at San Antonio; [3]Department of Pharmacology, University of Texas Health Science Center at San Antonio; [4]California Clinical Trials, Glendale, CA

The definition and assessment of adherence vary considerably across studies. Increasing consensus regarding these issues is necessary to improve our understanding of adherence and the development of more effective treatments. We review the adherence literature over the past 3 decades to explore the definitions and assessment of adherence to oral antipsychotics in schizophrenia patients. A total of 161 articles were identified through MEDLINE and PsycINFO searches. The most common method used to assess adherence was the report of the patient. Subjective and indirect methods including self-report, provider report, significant other report, and chart review were the only methods used to assess adherence in over 77% (124/161) of studies reviewed. Direct or objective measures including pill count, blood or urine analysis, electronic monitoring, and electronic refill records were used in less than 23% (37/161) of studies. Even in studies utilizing the same methodology to assess adherence, definitions of an adherent subject varied broadly from agreeing to take any medication to taking at least 90% of medication as prescribed. We make suggestions for consensus development, including the use of recommended terminology for different subject samples, the increased use of objective or direct measures, and the inclusion in all studies of an estimate of the percentage of medication taken as prescribed in an effort to increase comparability among studies. The suggestions are designed to advance the field with respect to both understanding predictors of adherence and developing interventions to improve adherence to oral antipsychotic medications.

Key words: adherence/oral antipsychotics/schizophrenia

[1]To whom correspondence should be addressed; Department of Psychiatry, University of Texas Health Science Center at San Antonio, Mail Code 7792, 7703 Floyd Curl Drive, San Antonio, TX 78229-3900, e-mail: velligand@uthscsa.edu.

Introduction

There is no question that adherence to medication is essential to maximizing outcomes for individuals with schizophrenia.[1,2] While adherence is poor across a wide variety of physical and psychiatric conditions,[1,3–5] the consequences of poor medication adherence can be devastating in schizophrenia, where the personal and societal costs of relapse are very high.[1,2] Although we continue to develop new antipsychotic and adjunctive treatments with broader efficacy and improved side-effect profiles, levels of adherence remain alarmingly low.[1,3]

For decades, researchers have worked to explain the causes of poor adherence and to develop interventions.[6–8] Unfortunately, there has been remarkably little agreement regarding the definition of adherence or how it is best measured. Medication adherence is often defined as ''the extent to which a person's behavior coincides with medical … advice.''[5(p2)] However, different operational definitions and different assessment methods identify different subgroups of patients. If the same patient can be identified as adherent in one study and nonadherent in the next, how are we to combine information across studies? If we continue to proceed as if we are speaking about the same thing when we use the term ''adherence,'' our efforts to understand and improve it are likely to remain largely unsuccessful. Changing our terms from ''noncompliance'' to ''adherence'' to ''concordance'' has served to promote the idea that medication treatment should be a collaborative effort between doctor and patient, but it has done little to address the fundamental methodological problems in adherence research. An agreed-upon set of definitions and a better understanding of the measurement problems and how to address them are necessary if we are going to unravel the complex nature of adherence and intervene effectively in schizophrenia. With these goals in mind, we review the literature on adherence to oral antipsychotics in schizophrenia patients over the past 3 decades.

Method

We searched the literature published between 1970 and February 2006 using both MEDLINE and PsycINFO for

articles containing the terms "adherence," "concordance." or "compliance" in combination with "schizophrenia." In addition, we utilized the reference sections of review articles to identify articles we may have missed using these search terms. We eliminated case studies, articles that did not include at least 1 measure of medication adherence, articles examining only or primarily depot medications, studies involving mainly inpatients who were administered medication during the time adherence was assessed, studies using dropout from a clinical drug trial as the primary measure of adherence, and review articles. We identified a total of 161 articles. A minimum of 2 investigators read all studies and agreed that the assessment of adherence for each study fit into 1 or more of the following discrete categories: self-report, significant other report, treatment provider report, chart review, pill count, electronic refill records, electronic monitoring, blood or urine levels, urine level of tracer substances, and ability to take medication. A priori we defined self-report, provider report (physician, nurse, or caseworker), and chart review as more subjective/indirect assessments of adherence, and pill counts, electronic monitoring, blood or urine sampling, and electronic refill records as either more objective or more direct measures. Chart review was not included as a direct/objective measure due to the heavy reliance on chart information in the report of the patient and opinion of the treatment provider. In addition, each author made a determination as to whether the article represented a specific adherence study. An investigation was classified as an adherence study if the goal were to identify predictors of adherence to oral medication, to examine relationships between adherence and other variables, to investigate the assessment of medication adherence, or to examine the effects of a treatment specifically designed to improve medication adherence. Using these criteria, studies examining the effects of family therapy on outcomes and those examining reasons for relapse were not classified specifically as adherence studies.

Results

Table 1 lists the identified studies, the number of subjects, the methods of assessing adherence, and the criteria used to define adherence. Of 161 studies that were identified, 93 were classified as specifically adherence studies, and 68 were classified as general studies that included a measure of adherence to oral antipsychotic medication. The most common method used to assess adherence in both general and adherence studies was the report of the patient. Self-report was utilized alone or in combination with other methods a total of 107 times in 161 studies. Moreover, 25% (17/68) of general studies and over 36% (34/93) of all studies that specifically examined adherence to medication used self-report as the sole assessment of medication adherence. Self-report methodologies themselves differed greatly among studies and included ad hoc measures, interview (unspecified), semistructured interviews (unspecified), and semistructured interviews using the Rating of Medication Influences (ROMI),[9] Treatment Compliance Interview (TCI),[9] Drug Attitude Inventory (DAI),[10] the medication compliance item from the Multnomah Community Ability Scale (MCAS),[11] Medication Adherence Rating Scale (MARS),[12] knowledge level, medication checklist, attitudes and insight, which asked subjects if there was a week or 2 weeks in the past variable period of time during which they stopped medication, and medication refusal.

Other methods were used less frequently. In order of frequency, methods were treatment provider report, family or significant other report, chart review, pill count, electronic refill information, electronic monitoring, blood level, urine analysis of medication, and urine analysis of a tracer substance. Figure 1 illustrates the specific frequencies of use of each method in the 161 studies. The subjective/indirect measures of assessing adherence were used 218 times (some studies used more than 1 of these methodologies) and were the only measures used in 124 of the 161 studies. Out of 161 studies, pill counts, blood levels, urine analysis, electronic monitoring, electronic refill records, or tracers that could provide objective or direct data regarding medication adherence were used only 43 times, representing a total of 37 of 161 studies. Of these 37 studies, 27 were specifically adherence studies and 10 were general studies. In one-fourth of these studies, the objective methodology was used only in part of the sample, only when reports by the patient were questioned (no criteria provided), only when the patient brought the urine or pills in to be examined, or only when available (usually with no information on how many subjects had such data available). One study used ability to take medication in a performance-based assessment.

Even in cases where studies used the same methodology to assess adherence, the definition of adherence varied greatly. Figure 2 describes the various levels of discrimination between adherence and nonadherence and the numerous ways to define nonadherence to oral medication. Any inception cohort of individuals for whom it is recommended that medication be taken continuously can be divided into those who refuse and those who accept medication. In a study using this first level of discrimination depicted in Figure 2, those who agree to take medication (accept) would be adherent, and all others would be considered nonadherent. For those who accept the medication, the next level divides subjects into those who continue to use it for a period of time and those who discontinue use for some time period, which varies across studies. At this level, those who discontinue use are nonadherent, all those who continue using the medication, even if dosages vary considerably from what is prescribed, are considered adherent. The next level of inquiry examines only those who

Table 1. Adherence Definitions and Methodology

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Abas et al. (2003)[14]	Reasons for admission to hospital, retrospective	225	Chart review	If stated and contributory to admission
Adams and Scott (2000)[15]	Predicting adherence using the Health Belief Model*	39	Self-report (ROMI, TRQ, rating from 0–100); all information used by rater	Highly adherent = >75%, partially adherent definitely = <70%, or uncertain adherence
Adams and Howe (1993)[16]	Predicting adherence, retrospective*	42	Self-report (medication taking behavior in the month prior to admission)	Self-rated: 0, 25, 50, 75, or 100%
Adewuya et al. (2006)[17]	Attitudes of outpatients in Nigeria*	312	Attitudes only (DAI)	DAI continuous variable
Agarwal et al. (1998)[18]	Factors contributing to noncompliance*	78	Self-report, significant other report, and provider report	Noncompliant = not taking medication, only took when had supply
Amador et al. (1993)[19]	Assessment of insight in psychosis	43	Self-report	4-point scale
Arango et al. (2006)[20]	Compare oral versus depot zuclopenthixol	46	Provider report (based on key informant and patient)	Adherence = 0%, 33%, 66%, or 100%, nonadherence = <33%
Ayers et al. (1984)[21]	Subjective response to antipsychotic medication	20	Self-report, provider report, UA (inpatient) self-report, family report, pill count (outpatient)	Noncompliant = 4 months and off medication during 9-month period
Bachmann et al. (2005)[22]	Neurological soft signs	39	Self-report	Dichotomous: regular intake vs not
Bechdolf et al. 2005[23]	Cognitive behavior therapy	88	Self-report, provider report, family report	Kemp 4-point scale: complete or partial refusal to active participation
Birchwood et al. (1992)[24]	Influence of ethnicity and family structure on relapse (retrospective)	137	Chart review (impression from outpatient appointments, small number cross-checked)	No criteria stated
Boczkowski et al (1985)[25]	Intervention to improve adherence*	36	Self-report, significant other report, pill count (brought in)	5-point scale, number missing/ number prescribed × 100
Brown et al. (1987)[26]	Factors related to adherence*	32	Self-report (to doctor and case manager), pill count (brought in monthly)	No information on scale for self-report; pills remaining in patient's allotment
Byerly et al. (2005)[27]	Clinician ratings versus MEMS*	25	Provider report; MEMS	7-point scale (Kemp); noncompliance = ≤4 at any month; daily adherence (MEMS) <70% during any month.
Byerly et al. (2005)[28]	Compliance therapy*	30	Self-report (MARS), clinician rating, MEMS	Days adherent based on openings vs prescribed for MEMS
Casper and Regan (1993)[29]	Reasons for admission	416	Self-report (retrospective)	Noncompliance = discontinued medication for 2 or more weeks prior to admission
Casper (1995)[30]	Identification of recidivists	45	Self-report (retrospective on admission), chart review	3 weeks+ without prescribed medication in the past 3 years
Chan (1984)[31]	Medication compliance in Chinese outpatients*	36	Self-report	Totally compliant or missed doses on ≤2 occasions vs noncompliant
Chen et al. (2005)[32]	First-episode patients	93	Provider report based on self-report and significant other report	Adherence = 70%+

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Christensen et al. (2006)[33]	Naturalistic study of patients on aripiprazole	42	Provider report	None set: informal impression of improved adherence
Christensen (1974)[34]	Factors influencing community success	126	Self-report	Not taken vs taken as prescribed (no cutoff defined)
Coldham et al. (2002)[35]	Prospective study of adherence in first-episode patients*	200	Chart review, provider report, dropout	3-point scale: nonadherent, inadequate (skipped but never longer than 2 weeks at a time), good (rarely or never missed)
Cuffel et al. (1996)[36]	Insight and adherence*	89	Self-report, significant other report	5-point scale: never missed to completely stopped
Conte et al. (1996)[37]	Intervention to improve adherence*	10	Self-report, significant other report (prior to previous hospitalizations)	No description of cutoff, but noncompliance reported as leading to hospitalization
Dani and Thienhaus (1996)[38]	Characteristics of patients in US and India	95	Self-report, significant other report	No criteria stated
Day et al. (2005)[39]	Attitudes toward medication*	228	Self-report (DAI, Morisky Compliance Scale)	Morisky = 4-item scale about forgetting or skipping; ordinal
Diaz et al. (2004)[40]	MEMS feasibility*	50	MEMS	% adherence = openings/ prescribed openings
Diaz et al. (2001)[13]	Prospective comparison of adherence*	14	MEMS	% adherence = openings/ prescribed openings
Dixon et al. (1997)[41]	Adherence and assertive community treatment*	77	Self-report, provider report, significant other report, pill count (subsample), blood level (subsample)	Noncompliant = refused or missed more than 1 week
Dolder et al. (2004)[42]	Assessment of medication beliefs*	63	Self-report (DAI, brief evaluation of medication influences and beliefs), refill record	Cumulative mean gap ratio, continuous
Donohoe et al. (2001)[43]	Predictors of compliance*	32	Self-report compliance interview (retrospective prior to hospitalization)	Poor = 0–25%, partial = 26–74%, good = 75%+
Dorevitch et al. (1993)[44]	Pharmacist medication maintenance program*	14	Self-report and missed appointments	Noncompliance = not taking oral medication, missed injection, missed appointments
Dossenbach et al. (2005)[45]	Schizophrenia Outpatient Health Outcomes study of antipsychotics	5833	Self-report (unclear measure)	% compliance
Drake et al. (1991)[46]	Housing instability	75	Provider report (rating)	Noncompliance = 4 or 5 on a 5-point scale
Drake and Wallach (1989)[47]	Substance abuse	187	Provider report (rating)	5-point scale
Duncan and Rogers (1998)[48]	Correlates of compliance*	90	Provider report (rating)	Compliant = 80%+, noncompliant = 50% or less, mixed group = 51–79%
Eaddy et al. (2005)[49]	Compliance and utilization*	7864	Electronic refill records	Compliance = 80–125%, partial compliance = <80%, overcompliance = >125%
Eckman et al. (1990)[50]	Intervention to improve adherence*	160	provider report, significant other report	% of medication taken as prescribed

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Elbogen et al. (2005)[51]	Depression and social stability as factors in nonadherence*	528	Self-report	1 = nonadherence, never compliant = 0, sometimes = 1, usually = 2, always = 3
Falloon et al. (1985)[52]	Family management	36	Self-report, provider report, significant other report, pill count, plasma levels	Irregular compliance = <75% of prescribed dose during each 1–2 month period
Farabee et al. (2004)[53]	Predictors of adherence among parolees*	150	Urine (metabolite indicating recent ingestion)	Presence vs absence
Favre et al. (1997)[54]	Expressed emotion and compliance*	59	Self-report, provider report	Discontinuing medication during 9-month follow-up
Fernando et al. (1990)[55]	Factors related to community tenure	70	Self-report	Excellent = 61–100%, moderate = 21–60%, poor = 0–20%
Fleischhacker et al. (2005)[56]	European first-episode trial	500	Self-report (DAI, Hayward)	Hayward 7-point scale, DAI continuous
Frangou et al. (2005)[57]	Telemonitoring of adherence*	108	MEMS and Internet monitor	% taken/prescribed over entire study period
Frank and Gunderson (1990)[58]	Therapeutic alliance	143	Self-report, provider report, chart review	Noncompliant = unilaterally altered dose, did not take full dose (cutoffs unclear)
Freudenreich et al. (2004)[59]	Attitudes, clinical variables, and insight*	81	Self-report (DAI)	DAI score
Gaebel et al. (2002)[60]	Intermittent vs continuous medication strategies	363	Provider report (rating)	4-point scale: 0 = good, 3 = bad
Gaebel and Pietzcker (1985)[61]	1-year outcome	72	Self-report and sometimes provider report (unclear when)	Whether medication taken continuously
Garavan et al. (1998)[62]	Relationships between compliance, attitudes, and insight*	82	Self-report (structured clinical interview retrospective over preceding 3 months)	4-point scale: 0–24%, 25–49%, 50–74%, 75+%; irregular compliance = <75%
Garcia-Cabeza et al. (2001)[63]	Prospective naturalistic study comparing medications	2657	Provider report	High = 80%, moderate = 60–79%, low = 20–59%, nil = <20%
Gilmer et al. (2004)[64]	Adherence to antipsychotics and health care costs*	2801	Electronic refill (Medi-Cal Database)	Cumulative possession ration (days medication available/ days eligible for Medi-Cal); nonadherent = 0–49%, partially adherent = 50–79%, adherent = 80–110%
Giron and Gomez-Beneyto (1995)[65]	Family attitudes and relapse	80	Self-report, significant other report	Poor compliance = 75% or less or if stopped for 1 month+
Giron and Gomez-Beneyto (1998)[66]	Family attitudes and relapse	80	Self-report, provider report, significant other report	Irregular compliance = <75 % or interrupted for 1 month+, noncompliant = failed to take medication 4 weeks+
Glick et al. (1991)[67]	Inpatient family intervention	169	Self-report, significant other report, provider report (if other reports unreliable)	6-point scale (unclear)
Glick and Berg (2002)[68]	Relapse and compliance with second-generation and first-generation antipsychotics*	996 and 339, 2 studies	Pill counts (between visits implied, unclear)	Examined time to first noncompliance; compliance = 80–120%
Godleski et al. (2003)[69]	Olanzapine therapy in patients previously taking depots	26	Self-report, pill count (brought in)	% taken as prescribed

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Gray et al. (2004)[70]	Medication management training for nurses	60	Self-report, provider report	7-point scale: 1 = complete refusal, 7 = active participation
Green (1988)[71]	Compliance and hospitalization*	50	Chart review	Identified in records as a precipitant to admission
Grunebaum et al. (2001)[72]	Medication supervision in residential care*	74	Self-report	Days not taken in past month
Grunebaum et al. (1999)[73]	Supported housing	36	Chart review	5-point scale: 0%, about 25%, about 50%, about 75%, all doses; compliant = took at least 50%
Guimâon (1995)[74]	Adherence intervention*	10	Self-report (ad hoc instruments)	4-point scale (unspecified)
Hamera et al. (1995)[75]	Substance abuse	17	Self-report (checklist)	Compliant = took all, some, or more than prescribed, noncompliant = did not take at all
Hayward (1995)[76]	Intervention to improve adherence*	21	Self-report (DAI), provider report, significant other report	7-point scale: complete refusal to active participation
Hertling et al. (2003)[77]	Comparison of flupenthixol and risperidone	144	Self-report (attitudes)	Change in DAI score
Hodgins et al. (2005)[78]	Conduct disorder in schizophrenia	248	Self-report (daily use), urine and hair analysis for substance use only	Report that patient took medication as prescribed
Hoffmann (1994)[79]	Factors related to rehospitalization	50	Provider report (rating)	6-point scale: 1 = low, 6 = high
Hogan et al. (1983)[80]	Self-report scale of compliance*	150	Self-report (DAI), provider report (rating)	7-point scale: habitual refusal to overrreliant on medication
Holzinger et al. (2002)[81]	Subjective illness theories of patients		Self-report at DC and 3 months	Percentage Adherence
Hornung et al. (1996)[82]	Psychoeducation*	191	Self-report, chart review	Dichotomized, but no specific criteria
Hunt et al. (2002)[83]	Compliance, substance abuse, and community survival*	99	Provider report, chart review (prescription data targeted)	% of medication
Ito and Oshima (1995)[84]	EE study	88	Provider report (rating)	Regular intake, irregular intake, injection, or refusal/cessation
Jarobe and Schartz (1999)[85]	Cognition and compliance*	8	Chart review (clinical trial, daily calendar of medication taken, so may have included pill count)	%
Jerrell (2002)[86]	Cost-effectiveness of medications	108	Chart review (including prescribing information)	%
Jeste et al. (2003)[87]	Cognitive impairment as predictor of adherence	110	Ability to take medication	Performance score
Joyce et al. (2005)[88]	Cost-effectiveness and compliance of medications*	1810	Electronic refill records	Medication possession ratio (days available/days prescribed), examined persistence
Kamali et al. (2006)[89]	Adherence in first episode*	100	Self-report, compliance interview	Nonadherent = 0–74%, adherent = 75%+
Kamali et al. (2001)[90]	Factors influencing compliance*	66	Self-report (structured interview), DAI	4-point scale:0–24%, 25–49%, 50–74%, 75+%; regular compliance = 75%+

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Kamali et al. (2000)[91]	Substance misuse and suicidal ideation	102	Self-report (structured interview)	Regular compliance = 75%+, others irregular
Kampman et al. (2004)[92]	Indicators of compliance in first episode*	80	Chart review	No specific information presented
Kampman et al. (2002)[93]	Indicators of compliance in first episode*	59	Self-report, pill count if subject did not ask for refill (no indication of *n* of subset)	Regular/irregular/discontinued
Kapur et al. (1992)[94]	Riboflavin marker in compliance assessment*	20	Urine analysis of tracer, provider report (rating)	Presence or absence in 18–24 hour period, visual analog 0–100
Kashner et al. (1991)[95]	Family characteristics related to hospitalization and substance abuse	121	Chart review (retrospective)	No criteria stated
Kelly et al. (1987)[96]	Health belief model and medication adherence*	107	Self-report (barriers and pill taking errors in past week)	Global score (continuous)
Kelly and Scott (1990)[97]	Intervention to improve adherence*	418	Self-report (pill taking errors in past week)	Discontinuation (present/absent), dosage deviation (present/absent)
Kemp et al. (1996)[98]	Adherence intervention* (continuation of above study)	47	Self-report (DAI), provider report, significant other report	7-point scale: complete refusal to active participation
Kemp et al. (1998)[99]		74	Self-report, provider report, significant other report (mean of 2 sources)	7-point scale: complete refusal to active participation
Kinon et al. (2003)[100]	Open label olanzapine disintegrating tablets	85	Self-report (ROMI, TCI), plasma levels taken but not used due to interpatient variability	Continuous
Kiraly et al. (1998)[101]	Risperidone treatment response	101	Provider report	4-point scale: poor to good
Klingberg et al. (1999)[102]	Psychoeducation*	156	Provider report (rating)	Dichotomized, but no specific criteria
Knapp et al. (2004)[103]	Nonadherence and cost*	658	Self-report (survey of residential facilities)	Taking less or more than prescribed
Koukia et al. (2005)[104]	Caregiver burden	134	Self-report, family report (unclear method)	Operational definition of medication compliance, variable unclear
Lecompte and Pelc (1996)[105]	Adherence intervention*	64	Self-report (unclear)	Noncompliant = minimum of 2 hospitalizations due to noncompliance; length of hospital stay postintervention
Li and Arthur (2005)[106]	Family education	101	Self-report	4-point scale; noncompliance = stopping for 1 week+ or change in dose against medical advice
Lin et al. (1979)[107]	Insight and adherence*	100	Self-report, provider or significant other report (as validation only)	Nonadherent = did not take, discontinued, other report rated as noncompliant
Linn et al. (1982)[108]	Relapse in foster care	151	Self-report, provider report	Taken as prescribed with supervision, taken as prescribed without supervision, probably not taken

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Linden et al. (2001)[109]	Predicting adherence*	122	Dropouts from medication treatment	Noncompliant = dropout
Lindstrom (1989)[110]	Retrospective clozapine efficacy	96	Self report, chart review	No specific information on cutoffs or definition
Linszen et al. (1998)[111]	Early intervention	76	Provider report (rating), pill counts (occasional?)	4-point scale: 0–24% (none/ irregular), 25–49% (rather irregular), 50–74% (rather regular), 75–100% (regular)
Loffler et al. (2003)[112]	Subjective reasons for compliance	307	Self-report (ROMI)	Scale score
Macpherson et al. (1997)[113]	Drug refusal*	54	Self-report (SAI), provider report, chart review	Active refusal, passive acceptance, active pursual; always, usually, not usually, never
Macpherson et al. (1996)[114]	Educational intervention*	64	Self-report (SAI)	Compliance subscale score
Marom et al. (2005)[115]	Expressed emotion and 1-year follow-up of next[116]	108	Self-report, chart review, recollection	Dichotomized at 50%
Marom et al. (2002)[116]	Expressed emotion	108	Self-report, chart review (prior to admission), anamnesis	Dichotomized at 50%
Martic-Biocina and Baric (2005)[117]	Assessment of reasons for stopping medication*	42	Self-report, reasons for stopping medication	No definition of compliance provided
McEvoy et al. (1984)[118]	Relapse and compliance*	32	Self-report, provider report, significant other report	Dichotomized; taken as prescribed most of the time during previous 2 months
McEvoy et al. (1989)[119]	Insight and psychopathology	52	Provider report (inpatient)	Active, passive, resistance, overt refusal
McFarlane et al. (1995)[120]	Multiple family group vs psychoeducation	172	Provider report (rating based on all available sources; unclear what other sources and how many)	6-point scale: 0, 25%, 50%, 75%, 90%, 100%
Menzin et al. (2003)[121]	Prospective over 1 year at start of medication	298	Electronic refill (Medicaid data)	Number of days medication available over 1-year follow-up; medication discontinued or switch
Merinder et al. (1999)[122]	Psychoeducation*	79	Chart review (prescribing information)	Noncompliant episode = no medication for 14 days; number of episodes
Nageotte et al. (1997)[123]	Health belief model and medication adherence*	101	Self-report, significant other report	Compliant = took all or missed only occasionally
Nakonezny and Byerly (2006)[124]	Adherence to first- and second-generation antipsychotics*	61	MEMS	Percentage; openings/prescribed for 1 month
Nelson et al. (1975)[125]	Variables related to compliance*	40	Urine analysis	Negative samples/total samples × 100
Ng et al. (2001)[126]	Expressed emotion	33	Provider report (rating) based on self-report and significant other report	4-point scale: 0–24% (none), 25–49% (irregular), 50–74% (vaguely regular), 75–100% (regular)
Norman and Malla (2002)[127]	Adherence, substance abuse, and psychosis*	90	Self-report, provider report (WQLS)	5-point scale: never to always
O'Donnell et al. (2003)[128]	Compliance therapy*	56	Self-report(structured interview), significant other report, provider report	0–24%, 25–49%, 50–74%, 75+%; compliance problem = <50%
Olfson et al. (2000)[129]	Prediction of noncompliance*	213	Self-report	Compliance = 1 week+ off medication

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Olfson et al. (1998)[130]	Inpatient and outpatient linkage*	104	Self-report	1 week+ off medication
Owen et al. (1996)[131]	Nonadherence and substance abuse*	135	Self-report	5-point scale: never missed to refused or stopped; compliant = rarely or never missed; those who rated 1 or 2 were "compliant," 3 and up were considered "noncompliant"
Parker and Hadzi-Pavlovic (1995)[132]	Life skills profile	118	Self-report, significant other report, provider report	Dichotomized but no specific information on how
Parkin et al. (1976)[133]	Adherence postdischarge	130	Self-report; pill count (in home)	Percentage deviation from prescribed; nonadherence = >15%
Pristach and Smith (1990)[134]	Compliance and substance abuse*	42	Self-report (chart review and information from significant other to verify; unclear how information used or how many had it)	Retrospective, not taking as prescribed prior to admission
Pyne et al. (2001)[135]	Charts of patients who do not believe they are ill	129	Self-report, significant other report	5-point scale: from never missed to completely stopped
Razali et al. (2000)[136]	Comparison of psychosocial interventions	143	Other report, pill count (doubtful cases only not specified)	Noncompliant, 25%, 50%, 75%, 90%, 100%; 90% considered ideal
Razali and Yahya (1995)[137]	Compliance intervention program*	225	Self-report	Good compliance = did not miss more than 2 doses on separate occasions, did not miss 2 consecutive doses in a 2-week period, and also attended all follow-ups or missed only 1; poor compliance = did not meet these criteria
Rettenbacher et al. (2004)[138]	Attitudes toward illness and medication*	61	Self-report (plasma levels taken but not used in analysis—states these agreed with adherence designation but not reported)	Fully compliant = none missed; partially compliant = no more than 7 consecutive days missed, or nonauthorized dose reduction during preceding 3 months; noncompliant = missed >7 days
Rijcken et al. (2004)[139]	Refill rate to assess compliance*	429	Electronic refill	Number of prescribed days/ calendar days; compliance = 90%+
Robinson et al. (2002)[140]	Predictors of medication discontinuation in first episode*	112	Self-report, family report, provider report	Stopping medication for 1 week+
Rosa et al. (2005)[141]	Factors related to compliance*	50	Self-report (ROMI), family report	Noncompliance = <75% in preceding 30 days
Rosenheck et al. (2000)[142]	Clozapine vs haloperidol	423	Pill count	Medication continuation and regimen compliance
Ruscher et al. (1997)[143]	Compliance and attitudes*	148	Self-report	Noncompliant = dose or timing differences from prescribed, or discontinuation
Rzewuska (2002)[144]	Compliance and course*	94	Self-report	Time taken during remission vs time not taken during remission

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Sellwood and Tarrier (1994)[145]	Demographics as predictor of noncompliance*	256	Provider report	Noncompliant = persistently refused all medication, vs all others
Sellwood et al. (2001); Sellwood et al. (2003)[146,147]	Family intervention and compliance* (2003)	79	Self-report, chart review	<10%, 10–50%, 50–90%, 90%+; compliant = 90%+
Seo and Min (2005)[148]	Explanatory model of adherence*	208	Self-report, family report	% compliance continuous variable, no cutoff
Seltzer et al. (1980)[149]	Psychoeducation*	52	Pill count and urine (brought in; n = 32)	Compliant = positive urine, 80% of pills taken
Serban and Thomas (1974)[150]	Attitudes toward ambulatory treatment	641	Self-report, significant other report (SSFIPD)	Regular compliance vs irregular; cutoff not provided
Shvartsburd et al. (1984)[151]	Blood levels in maintenance treatment	21	Self-report, pill count, blood	No specific information on cutoffs or criteria
Sibitz et al. (2005)[152]	Attitudes toward medication*	92	Self-report (DAI)	Dichotomized based on DAI
Smith et al. (1997)[153]	Insight and compliance*	33	Self-report, chart review, significant other report	% taken correctly
Sullivan et al. (1995)[154]	Risk factors for hospitalization	101	Self-report, significant other report, chart review	Noncompliant = taken <50%; self-report unless conflicted with report of significant other
Suzuki et al. (2005)[155]	Simplifying medication regimen*	50	Treatment provider report	At least partially compliant vs not at all
Svarstad et al. (2001)[156]	Adherence and hospitalization*	619	Electronic refill (Medicaid claims)	Regular vs irregular users based on claim missed for 1 quarter
Svedberg et al. (2001)[157]	First-episode patients	71	Chart review (prescribing information)	Noncompliant = too much or too little medication; totally noncompliant = refused
Swanson et al. (2004)[158]	Atypicals and violence	229	Self-report	5-point scale: never missed to completely stopped
Thompson et al. (2000)[159]	Adherence rating scale*	66	Self-report (DAI and MAQ), provider ratings (where available), blood level (n = 17, lithium only)	Scale score: noncompliant = 0, compliant = 1
Trauer and Sacks (1998)[160]	Compliance views of clients and doctors*	254	Self-report, provider report (rating)	Active, passive, resistance, refusal; 0%, 25%, 50%, 75%, 100%
Valenstein et al. (2001)[161]	Adherence and depot medication	1307	Provider report	All, most, quite a bit, some, none; strict compliance = all; broad compliance = all or most
Van Putten et al. (1976)[162]	Drug refusal*	59	Provider report (rating)	Dichotomized into refusers and compliers (anyone not refusing)
Vaughan et al. (2000)[163]	Community treatment orders	246	Self-report, significant other report, chart review	Number of days of noncompliance prior to admission
Vauth et al. (2004)[164]	Adherence assessment*	184	Self-report (ROMI)	4-point scale
Velligan et al. (2003)[1]	Adherence*	68	Self-report, pill count, blood levels	5-point scale: compliant = 80%, blood level consistency
Verghese et al. (1989)[165]	Course and outcome	323	Self-report (unspecified)	Regular vs irregular compliers (unspecified)
Weiden et al. (1995)[166]	Postdischarge compliance*	93	Self-report (TCI, ROMI)	5-point scale: completely noncompliant to completely compliant

Table 1. Continued

Author(s)	Study Description*	N	Adherence Assessment	Criteria for Adherence
Weiden et al. (2004b)[167]	Compliance and obesity*	304	Self-report	5-point scale: never missing to almost always; compliant = never missing, noncompliant = all others
Weiden et al. (2004a)[168]	Partial compliance and rehospitalization*	4325	Electronic refill (Medicaid data)	Gaps in therapy, number of mean gaps, mean gap duration, consistency, persistence
Weiss et al. (2002)[169]	Predictors of nonadherence*	162	Provider report	4-point scale: active, passive, resistant, refusal; dichotomized into active adherence vs problem
Xiong et al. (1994)[170]	Family intervention	63	Significant other report	Compliant = took >50% of medication for 75% of follow-up period
Yamada et al. (2006)[171]	Reasons for noncompliance*	90	Self-report (ROMI)	Noncompliance = 1-week interruption during follow-up period
Yen et al. (2005)[172]	Compliance and insight*	139	Self-report (SAI and ad hoc Medication Adherence Behavior Scale)	Continuous
Ziguras et al. (2001)[173]	Influences of medication compliance	168	Self-report (MCAS)	5-point scale: almost never complies to almost always complies; poor adherence = <30%

Note: *Specific Adherence Study; DC = discharge; EE = Expressed Emotion; MAQ = Medication Adherence Questionnaire; SAI = Schedule for the Assessment of Insight; SSFIPD = Social Stress and Functioning Inventory in Psychotic Disorders; TRQ = Tablets Routine Questionnaire; UA = Urine Analysis; WQLS = Wisconsin Quality of Life Scale.

continue to take medication. These individuals may take medication as prescribed or not. How much an individual can vary from the prescribed dosage and still be considered compliant differs by study. Dosage deviations can be due to a decision that less medication is better, due to unintentional factors such as forgetting, or due to environmental barriers such as poverty and lack of transportation.

With respect to dosage deviation, in the 161 articles we found dosage cutoffs that ranged from 50% to 90% and categorical classifications ranging from taking any of the prescribed medication to taking nearly every dose. Likert-type scales that were not divided into percentage of medication taken varied from 3 points to 7 points, with a variety of different terms for each point, including "overreliance on medication" at the high end of 1 scale.

For electronic refill data, a common adherence measure was the mean gap or the length of time for which no medication was available to the patient. An alternative measure examined patients who had gone a quarter without a claim for medication.

Several studies reported using Medication Event Monitoring System, or MEMS—pill bottle caps capable of recording the time and date each time the bottle is opened. Openings for other reasons (eg, filling), if known to the researchers, must be deleted to provide an accurate estimate of the number of doses taken. While MEMS is sometimes described as a "gold standard" of adherence assessment, in the studies using MEMS for schizophrenia patients, the fact of missing data was identified as a problem.

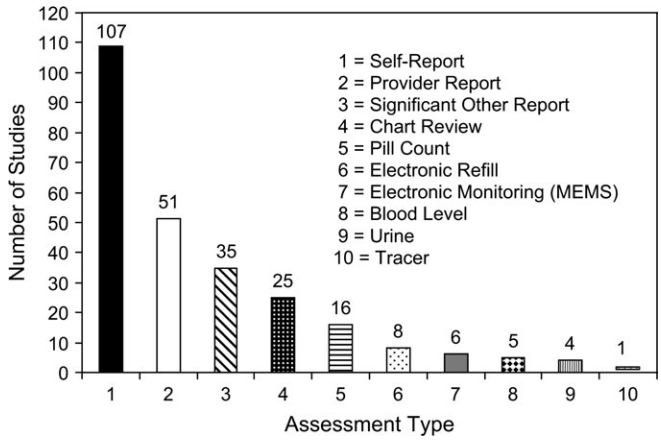

Fig. 1. Number of Times Specific Adherence Methodologies Have Been Utilized.

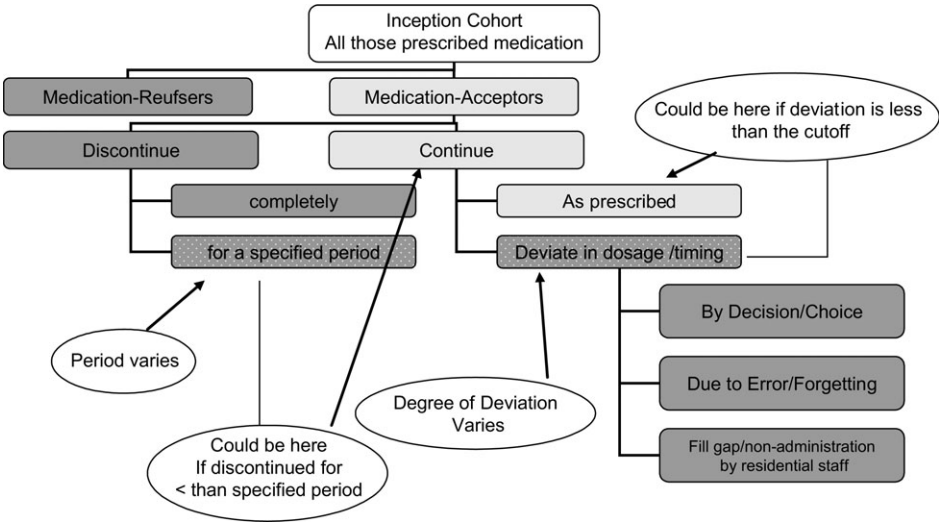

Fig. 2. Defining Subjects in Adherence Studies.

One study reported close to 45% of data missing due to failures on the part of the patient to bring in the MEMS caps in order to download the information.[13]

Discussion

The review illustrates the heavy reliance in the field on self-report and other subjective/indirect measures of adherence, which are known to be significantly flawed. Unfortunately, each method used to assess adherence to oral medications in this population has its own drawbacks. Self-report often exaggerates the degree of adherence. A commonly cited quotation from subjects regarding self-report of adherence behavior goes as follows: ''How do you expect me to remember when I forget to take my medication?'' Provider report may be based on the report of the patient or on a worsening clinical condition, which may be related either to poor adherence or to a failure of the chosen medication to control symptoms. The report of significant others is affected by how much time the respondent spends with the identified subject and how directly involved the significant other may be in the subject's care. This method cannot be used when patients do not have sufficiently involved informants. Studies using chart review often did not specify the information available in the chart to make a determination about adherence. References to medication adherence in the chart may turn out to be based largely on self-report.

More direct or objective measures of assessment also have problems. Pill counts and refill records can be affected by the use of samples and old medications that are still available to the patient. Pill counts are often complicated by medication from earlier time periods that are added to current prescription bottles. This leaves the researcher with more pills to count than the number indicated on the bottle as dispensed by the pharmacy. Most studies reviewed expected patients to bring in bottles for the pill count; some required patients to bring in urine samples or electronic monitors (MEMS caps). This methodology is likely to bias results toward finding higher levels of compliance. Electronic monitoring can also be problematic when subjects do not replace the caps or take medication out of alternative bottles. While electronic monitoring is considered a gold standard in adherence research with other populations, the cognitive impairments and unstable living environments often found in patients with schizophrenia may make it necessary to use alternative methodologies such as home visits to retrieve MEMS data or using a system that automatically downloads adherence information.[57,174]

Electronic prescribing records provide an objective assessment of the medication obtained by the patient. Unfortunately, just because medication is available does not mean that it is taken. While this method is likely to underreport problems with adherence, utilizing electronic refill data in large samples can provide substantial power to examine relationships between adherence and outcomes from a cost perspective. Certain assumptions must be made in utilizing such data (eg, that prescriptions are not filled outside of the system). In addition, decisions must be made regarding how to deal with subjects taking more than 1 antipsychotic medication (eg, delete all subjects with multiple antipsychotic prescriptions during the specified period). Accuracy problems may occur when subjects are given unrecorded samples, when medications are filled outside the system, and when old medications from prior episodes of poor adherence are available to the patient.

Even blood levels cannot be considered a gold standard for adherence as they can be highly affected by behaviors in the days immediately prior to the blood draw. Thus, the sample obtained may not represent the level of

adherence over a more extended time period (1 month, 3 months). Moreover, there is a great deal of individual variability in blood levels across patients. With the atypical antipsychotic medications there is very little data about appropriate or therapeutic blood levels to use as a criterion.[100] In fact, in a recent study of olanzapine, blood levels were taken but not used as the primary measure of adherence for this reason.[100] Obviously, the more intrusive or elaborate the method of adherence assessment, the more it will deviate from clinical practice and be less appropriate for use by practicing clinicians. Moreover, some adherence assessments can influence adherence behavior.

Few studies appropriately critique their own methods for assessing adherence or point out the problems encountered in obtaining the data using the chosen method(s). This can make it somewhat unclear whether the conclusions of the studies are fully supported by the data presented.

With respect to the definition of adherence, the field may not have as many definitions as studies, but the number of definitions is clearly problematic. More often than not, the definitions and rationales for the choices are not clearly explained. Because definitions differ, the same subject could be categorized differently depending on the study. For example, a patient who takes about 55% of his or her antipsychotic medication would be classified as adherent in a study examining medication refusal as the criterion for nonadherence. This same patient would be classified as nonadherent if he or she discontinued medication for at least a 1-week period in a study using this as the method to define the nonadherent group. In a study using a cutoff of taking at least 50% of medication, this patient would fall into the adherent group, even if he or she did not take any medication for a 1-week period because the measure used averages over a period of 1 month. The same patient would be nonadherent in a study using a higher cutoff percentage during the specified time period.

What is an appropriate percentage of medication for an individual to take before he or she is considered poorly adherent? Based on the review, the answer to this question is far from clear. Percentage of medication taken as prescribed could be used as a continuous variable. However, the percentage may have high variability, necessitating very large sample sizes before statistical significance could be found in treatment studies in which a treatment would have a moderate effect. In addition, the difference between taking 0% versus 25% or 80% versus 100% of prescribed medication may not be clinically significant. Therefore, grouping subjects into clusters of 0 to 29%, 30–69%, and 70–75%+ may make conceptual sense. Part of the difficulty may be that each investigator examines their data and chooses cut points based on natural breaks in their data. Arbitrarily choosing 80% as a cutoff for adherence may yield no adherent patients in some studies.

The issue of percentage of medication taken as prescribed to classify adherence is further complicated by the tendency over time for physicians to increase the dosage of medication when symptoms are not well controlled. Over time, dosages can creep up because patients are not fully adherent, making the full dose clinically inappropriate when the patient is taking medication as prescribed.

It is common to validate adherence measures against clinical outcome. This is best seen in studies of electronic pharmacy records in which gaps in having medication available predict hospitalization. However, there may be problems in using some clinical outcome data to validate adherence measures. It is not uncommon for treating physicians to base their impression of adherence on clinical state (symptomatology, clinical global impression). Therefore, it is possible that physician-rated adherence would have a stronger relationship with clinical state than adherence assessed through more objective means. It is also true that we do not know the clinical consequences of many types of nonadherence.

Suggestions for Consensus Development

Definitions

Given the confusion in the field, we would propose defining those who do not accept medication as ''medication refusers'' to distinguish them from individuals who continue to take medication but may have adherence problems. This latter group of medication acceptors can then be further divided by degrees of adherence. This is important because complete refusal may begin as a function of missed or skipped doses, either intentional or accidental. It is likely that what predicts medication refusal and what predicts irregular compliance, or what we call ''dosage deviation,'' may be very different. It is also likely that treatment approaches to these 2 groups of individuals may need to target very different variables, insight in the former case and cognitive deficits or environmental problems in the latter. It is unclear how patients who discontinue the use of medication for 1 week or longer compare with those who somewhat consistently take half of their prescribed dosage. Moreover, it is likely to be very important to distinguish those who deviate in dosage by choice versus those who inadvertently miss medication due to forgetting, misunderstanding, poverty, or other environmental barriers. The focus of intervention for these groups could vary considerably.

Study Design

Prospective studies that follow patients over time and examine adherence are necessary to determine predictors of problem adherence. The difficulties with retrospective data, particularly in the schizophrenia population, are

numerous and include problems with inaccurate recall and backward reasoning ("I got sick, so I must have forgotten to take my medication"). Longer follow-up periods are likely to minimize the impact of assessing adherence on adherence behavior.

Comparability Among Studies

To increase comparability among studies, it would be helpful for each investigation to report an estimate of the mean percentage of medication taken during the follow-up period, even if the primary measure of adherence is operationalized otherwise. This would allow studies to be compared on a common variable. At the same time, this would allow investigators to group patients according to natural breaks in their data and the overall adherence level in their samples.

Assessment

We would suggest that all studies include at least 2 measures of adherence and that at least 1 of these be a direct or objective measure such as pill count, urine analysis, blood analysis (if problems discussed below have been addressed), electronic monitoring, pharmacy refill records, or the examination of tracer substances in blood or urine. Pharmacy refill records have been found to be useful for large samples, but it is unclear whether this method will be sensitive in smaller samples investigating the effects of clinical treatment. While it may be economically prohibitive in some studies and inconvenient in all studies, doing pill counts, downloading electronic monitoring devices, and collecting blood or urine are likely to be best accomplished during home visits. We have been able to decrease loss of data to less than 5% by downloading MEMS information from the caps on home visits using laptop computers. Alternatively, using more sophisticated electronic devices such as the MedeMonitor[174] is recommended. This device records the same type of data as MEMS but stores up to 5 different medications. Using an LCD readout, the monitor can query the subject as to whether a specific compartment has been opened for the purpose of taking medication or for some other reason. Most important, the monitor downloads adherence data automatically to a secure Web site, decreasing problems with data retrieval.[174]

An in-home setup at the beginning of studies that use electronic monitoring and pill counts can cut down on problems. For example, extra medications can be bagged and stapled and only recounted if the seal is broken. A box can be provided for patients to store empty bottles, making determinations of pills dispensed more accurate over time. Pill counts should be cross-referenced with prescribing records to deal with some of the problems described above, such combining bottles together. Training on the use of electronic monitoring devices, providing belt bags to carry the larger electronic pill containers, and using the more sophisticated devices may advance the field.

Because there is so much variability in blood-level data from patient to patient for the atypical antipsychotic medications, if blood samples are collected, obtaining individualized baseline levels during a period in which all medication taking is monitored may be ideal. Randomly drawn blood levels during a follow-up period can then be compared with the baseline levels for consistency between consecutive levels and consistency in plasma level/dose. However, unless better procedures for interpreting blood-level data become available in the near future for the atypical antipsychotic medications, it is unclear how blood-level data will assist the field in better understanding adherence.

The use of multivariable algorithms that combine measures to make a determination of adherence level needs further investigation. One approach would involve assessing larger samples of patients with multiple measures of adherence. With samples approaching 200, factor analytic techniques could be used to determine whether adherence could be conceptualized as a latent variable in which the various sources of error could be explicitly modeled.

While the assessment of the ability to take medication is important for this population, the ability to perform a task does not always translate into performing the task in the natural environment. Because adherence problems are likely to be multidetermined in the natural environment, the usefulness of ability as a proxy for actual adherence may be limited.

Irrespective of method, we recommend briefly describing the reasons for selection of the method, the pros and cons of the method selected, and the actual problems encountered in obtaining the data. For example, a recent study by Grymonpre et al.[4] in an elderly population describes the problems encountered in their sample while obtaining pill counts. Including this type of information in a report would assist readers in evaluating the conclusions of the study.

In summary, to be successful in identifying predictors of adherence and developing interventions we need to do better in defining and assessing adherence. By putting into place some standardization of terms and procedures, the field is more likely to accomplish these goals. These suggestions for consensus development most closely apply to adherence to oral antipsychotic medications in psychosis patients. However, given that the vast majority of prescriptions for atypical antipsychotic medications are "off-label," the problems in assessment and the recommendations made may be relevant for a wider range of populations.

Acknowledgments

Dr. Velligan, Dr. Lam, Dr. Ereshefsky, and Dr. Miller were supported in part during the writing of this paper

by National Institutes of Mental Health grant R01 MH62850-05. Dr. Velligan, Dr. Miller, and Dr. Glahn were supported in part during the writing of this paper by National Institutes of Mental Health grant R01 MH61775-04.

References

1. Velligan DI, Lam F, Ereshefsky L, Miller AL. Psychopharmacology: perspectives on medication adherence and atypical antipsychotic medications. *Psychiatr Serv.* 2003;54: 665–667.
2. Weiden P, Glazer W. Assessment and treatment selection for ''revolving door'' inpatients with schizophrenia. *Psychiatr Q.* 1997;68:377–392.
3. Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiatry.* 2002;159:103–108.
4. Grymonpre RE, Didur CD, Montgomery PR, Sitar DS. Pill count, self-report, and pharmacy claims data to measure medication adherence in the elderly. *Ann Pharmacother.* 1998;32:749–754.
5. Haynes RB. Introduction. In: Sackett DL, Taylor DW, eds. *Compliance in Health Care* Baltimore, MD: Johns Hopkins University Press; 1979.
6. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull.* 1997;23:637–651.
7. Oehl M, Hummer M, Fleischhacker WW. Compliance with antipsychotic treatment. *Acta Psychiatr Scand.* 2000;102(suppl): 83–86.
8. Zygmunt A, Olfson M, Boyer CA, Mechanic D. Interventions to improve medication adherence in schizophrenia. *Am J Psychiatry.* 2002;159:1653–1664.
9. Weiden P, Rapkin B, Mott T, et al. Rating of Medication Influences (ROMI) scale in schizophrenia. *Schizophr Bull.* 1994;20:297–310.
10. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med.* 1983;13: 177–183.
11. Barker S, Barron N, McFarland B, Bigelow D. A community ability scale for chronically mentally ill consumers: part I. reliability and validity. *Community Ment Health J.* 1994;30(4):363–383.
12. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res.* 2000;42:241–247.
13. Diaz E, Levine HB, Sullivan MC, et al. Use of the Medication Event Monitoring System to estimate medication compliance in patients with schizophrenia. *J Psychiatry Neurosci.* 2001;26:325–329.
14. Abas M, Vanderpyl J, Le Prou T, Kydd R, Emery B, Foliaki SA. Psychiatric hospitalization: reasons for admission and alternatives to admission in South Auckland, New Zealand. *Aust N Z J Psychiatry.* 2003;37:620–625.
15. Adams J, Scott J. Predicting medication adherence in severe mental disorders. *Acta Psychiatr Scand.* 2000;101:119–124.
16. Adams SG Jr, Howe JT. Predicting medication compliance in a psychotic population. *J Nerv Ment Dis.* 1993;181: 558–560.
17. Adewuya AO, Ola BA, Mosaku SK, Fatoye FO, Eegunranti AB. Attitude towards antipsychotics among outpatients with schizophrenia in Nigeria. *Acta Psychiatr Scand.* 2006; 113:207–211.
18. Agarwal MR, Sharma VK, Kishore Kumar KV, Lowe D. Non-compliance with treatment in patients suffering from schizophrenia: a study to evaluate possible contributing factors. *Int J Soc Psychiatry.* 1998;44:92–106.
19. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. *Am J Psychiatry.* 1993;150:873–9.
20. Arango C, Bombín I, González-Salvador T, García-Cabeza I, Bobes J. Randomised clinical trial comparing oral versus depot formulations of zuclopenthixol in patients with schizophrenia and previous violence. *Eur Psychiatry.* 2006; 21:34–40.
21. Ayers T, Liberman RP, Wallace CJ. Subjective response to antipsychotic drugs: failure to replicate predictions of outcome. *J Clin Psychopharmacol.* 1984;4:89–93.
22. Bachmann S, Bottmer C, Schroder J. Neurological soft signs in first-episode schizophrenia: a follow-up study. *Am J Psychiatry.* 2005;162:2337–2343.
23. Bechdolf A, Kohn D, Knost B, Pukrop R, Klosterkotter J. A randomized comparison of group cognitive-behavioral therapy and group psychoeducation in acute patients with schizophrenia: outcome at 24 months. *Acta Psychiatr Scand.* 2005;112:173–179.
24. Birchwood M, Cochrane R, Macmillan F, Copestake S, Kucharska J, Carriss M. The influence of ethnicity and family structure on relapse in first-episode schizophrenia: a comparison of Asian, Afro-Caribbean, and white patients. *Br J Psychiatry.* 1992;161:783–790.
25. Boczkowski JA, Zeichner A, DeSanto N. Neuroleptic compliance among chronic schizophrenic outpatients: an intervention outcome report. *J Consult Clin Psychol.* 1985;53: 666–671.
26. Brown CS, Wright RG, Christensen DB. Association between type of medication instruction and patients' knowledge, side effects, and compliance. *Hosp Community Psychiatry.* 1987;38:55–60.
27. Byerly M, Fisher R, Whatley K, et al. A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. *Psychiatry Res.* 2005; 133:129–133.
28. Byerly MJ, Fisher R, Carmody T, Rush AJ. A trial of compliance therapy in outpatients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2005;66:997–1001.
29. Casper ES, Regan JR. Reasons for admission among six profile subgroups of recidivists of inpatient services. *Can J Psychiatry.* 1993;38:657–661.
30. Casper ES. Identifying multiple recidivists in a state hospital population. *Psychiatr Serv.* 1995;46:1074–1075.
31. Chan DW. Medication compliance in a Chinese psychiatric out-patient setting. *Br J Med Psychol.* 1984;57:81–89.
32. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. *Schizophr Res.* 2005;77(1): 99–104.
33. Christensen AF, Poulsen J, Nielsen CT, Bork B, Christensen A, Christensen M. Patients with schizophrenia treated with aripiprazole, a multicentre naturalistic study. *Acta Psychiatr Scand.* 2006;113:148–153.

34. Christensen JK. A 5-year follow-up study of male schizophrenics: evaluation of factors influencing success and failure in the community. *Acta Psychiatr Scand.* 1974;50:60–72.
35. Coldham EL, Addington J, Addington D. Medication adherence of individuals with a first episode of psychosis. *Acta Psychiatr Scand.* 2002;106:286–290.
36. Cuffel BJ, Alford J, Fischer EP, Owen RR. Awareness of illness in schizophrenia and outpatient treatment adherence. *J Nerv Ment Dis.* 1996;184:653–659.
37. Conte G, Ferrari R, Guarneri L, Calzeroni A, Sacchetti E. Reducing the "revolving door" phenomenon. *Am J Psychiatry.* 1996;153:1512.
38. Dani MM, Thienhaus OJ. Characteristics of patients with schizophrenia in two cities in the U.S. and India. *Psychiatr Serv.* 1996;47:300–301.
39. Day JC, Bentall RP, Roberts C, et al. Attitudes toward antipsychotic medication: the impact of clinical variables and relationships with health professionals. *Arch Gen Psychiatry.* 2005;62:717–724.
40. Diaz E, Neuse E, Sullivan MC, Pearsall HR, Woods SW. Adherence to conventional and atypical antipsychotics after hospital discharge. *J Clin Psychiatry.* 2004;65:354–360.
41. Dixon L, Weiden P, Torres M, Lehman A. Assertive community treatment and medication compliance in the homeless mentally ill. *Am J Psychiatry.* 1997;154:1302–1304.
42. Dolder CR, Lacro JP, Warren KA, Golshan S, Perkins DO, Jeste DV. Brief evaluation of medication influences and beliefs: development and testing of a brief scale for medication adherence. *J Clin Psychopharmacol.* 2004;24:404–409.
43. Donohoe G, Owens N, O'Donnell C, et al. Predictors of compliance with neuroleptic medication among inpatients with schizophrenia: a discriminant function analysis. *Eur Psychiatry.* 2001;16:293–298.
44. Dorevitch A, Aronzon R, Zilberman L. Medication maintenance of chronic schizophrenic out-patients by a psychiatric clinical pharmacist: 10-year follow-up study. *J Clin Pharm Ther.* 1993;18:183–186.
45. Dossenbach M, Arango-Davila C, Ibarra HS, et al. Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine, or haloperidol: 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *J Clin Psychiatry.* 2005;66:1021–1030.
46. Drake RE, Wallach MA, Teague GB, Freeman DH, Paskus TS, Clark TA. Housing instability and homelessness among rural schizophrenic patients. *Am J Psychiatry.* 1991;148: 330–336.
47. Drake RE, Wallach MA. Substance abuse among the chronic mentally ill. *Hosp Community Psychiatry.* 1989;40:1041–1046.
48. Duncan JC, Rogers R. Medication compliance in patients with chronic schizophrenia: implications for the community management of mentally disordered offenders. *J Forensic Sci.* 1998;43:1133–1137.
49. Eaddy M, Grogg A, Locklear J. Assessment of compliance with antipsychotic treatment and resource utilization in a Medicaid population. *Clin Ther.* 2005;27(2):263–272.
50. Eckman TA, Liberman RP, Phipps CC, Blair KE. Teaching medication management skills to schizophrenic patients. *J Clin Psychopharmacol.* 1990;10:33–38.
51. Elbogen EB, Swanson JW, Swartz MS, Van Dorn R. Medication non-adherence and substance abuse in psychotic disorders: impact of depressive symptoms and social stability. *J Nerv Ment Dis.* 2005;193:673–679.
52. Falloon IR, Boyd JL, McGill CW, et al. Family management in the prevention of morbidity of schizophrenia: clinical outcome of a two-year longitudinal study. *Arch Gen Psychiatry.* 1985;42:887–896.
53. Farabee D, Shen H, Sanchez S. Program-level predictors of antipsychotic medication adherence among parolees. *Int J Offender Ther Comp Criminol.* 2004;48:561–571.
54. Favre S, Huguelet MA, Vogel S, Gonzalez MA. Neuroleptic compliance in a cohort of first episode schizophrenics: a naturalistic study. *Eur J Psychiatry.* 1997;11:35–42.
55. Fernando ML, Velamoor VR, Cooper AJ, Cernovsky Z. Some factors relating to satisfactory post-discharge community maintenance of chronic psychotic patients. *Can J Psychiatry.* 1990;35:71–73.
56. Fleischhacker WW, Keet IP, Kahn RS. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. *Schizophr Res.* 2005;78(2–3):147–156.
57. Frangou S, Sachpazidis I, Stassinakis A, Sakas G. Telemonitoring of medication adherence in patients with schizophrenia. *Telemed J E-Health.* 2005;11(6):675–683.
58. Frank AF, Gunderson JG. The role of the therapeutic alliance in the treatment of schizophrenia: relationship to course and outcome. *Arch Gen Psychiatry.* 1990;47:228–236.
59. Freudenreich O, Cather C, Evins AE, Henderson DC, Goff DC. Attitudes of schizophrenia outpatients toward psychiatric medications: relationship to clinical variables and insight. *J Clin Psychiatry.* 2004;65:1372–1376.
60. Gaebel W, Janner M, Frommann N, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. *Schizophr Res.* 2002; 53:145–159.
61. Gaebel W, Pietzcker A. One-year outcome of schizophrenic patients: the interaction of chronicity and neuroleptic treatment. *Pharmacopsychiatry.* 1985;18:235–239.
62. Garavan J, Browne S, Gervin M, Lane A, Larkin C, O'Callaghan E. Compliance with neuroleptic medication in outpatients with schizophrenia: relationship to subjective response to neuroleptics; attitudes to medication and insight. *Compr Psychiatry.* 1998;39:215–219.
63. Garcia-Cabeza I, Gomez JC, Sacristan JA, Edgell E, Gonzalez de Chavez M. Subjective response to antipsychotic treatment and compliance in schizophrenia: a naturalistic study comparing olanzapine, risperidone and haloperidol (EFESO Study). *BMC Psychiatry.* 2001;1:7.
64. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry.* 2004;161:692–699.
65. Giron M, Gomez-Beneyto M. Relationship between family attitudes measured by the semantic differential and relapse in schizophrenia: a 2 year follow-up prospective study. *Psychol Med.* 1995;25:365–371.
66. Giron M, Gomez-Beneyto M. Relationship between empathic family attitude and relapse in schizophrenia: a 2-year follow-up prospective study. *Schizophr Bull.* 1998; 24:619–627.
67. Glick ID, Clarkin JF, Haas GL, Spencer JH Jr, Chen CL. A randomized clinical trial of inpatient family intervention: VI. mediating variables and outcome. *Fam Process.* 1991;30: 85–99.
68. Glick ID, Berg PH. Time to study discontinuation, relapse, and compliance with atypical or conventional antipsychotics

in schizophrenia and related disorders. *Int Clin Psychopharmacol.* 2002;17:65–68.

69. Godleski LS, Goldsmith LJ, Vieweg WV, Zettwoch NC, Stikovac DM, Lewis SJ. Switching from depot antipsychotic drugs to olanzapine in patients with chronic schizophrenia. *J Clin Psychiatry.* 2003;64:119–122.
70. Gray R, Wykes T, Edmonds M, Leese M, Gournay K. Effect of a medication management training package for nurses on clinical outcomes for patients with schizophrenia: cluster randomised controlled trial. *Br J Psychiatry.* 2004; 185:157–162.
71. Green JH. Frequent rehospitalization and noncompliance with treatment. *Hosp Community Psychiatry.* 1988;39: 963–966.
72. Grunebaum MF, Weiden PJ, Olfson M. Medication supervision and adherence of persons with psychotic disorders in residential treatment settings: a pilot study. *J Clin Psychiatry.* 2001;62:394–399.
73. Grunebaum M, Aquila R, Portera L, Leon AC, Weiden P. Predictors of management problems in supported housing: a pilot study. *Community Ment Health J.* 1999;35:127–133.
74. Guimâon J. The use of group programs to improve medication compliance in patients with chronic diseases. *Patient Educ Couns.* 1995;26:189–193.
75. Hamera E, Schneider JK, Deviney S. Alcohol, cannabis, nicotine, and caffeine use and symptom distress in schizophrenia. *J Nerv Ment Dis.* 1995;183:559–565.
76. Hayward P. Medication self-management: a preliminary report on an intervention to improve medication compliance. *J Ment Health.* 1995;4:511–518.
77. Hertling I, Philipp M, Dvorak A, et al. Flupenthixol versus risperidone: subjective quality of life as an important factor for compliance in chronic schizophrenic patients. *Neuropsychobiology.* 2003;47:37–46.
78. Hodgins S, Tiihonen J, Ross D. The consequences of conduct disorder for males who develop schizophrenia: associations with criminality, aggressive behavior, substance use, and psychiatric services. *Schizophr Res.* 2005;78: 323–335.
79. Hoffmann H. Age and other factors relevant to the rehospitalization of schizophrenic outpatients. *Acta Psychiatr Scand.* 1994;89:205–210.
80. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. *Psychol Med.* 1983;13:177–183.
81. Holzinger A, Loffler W, Muller P, Priebe S, Angermeyer MC. Subjective illness theory and antipsychotic medication compliance by patients with schizophrenia. *J Nerv Ment Dis.* 2002;190:597–603.
82. Hornung WP, Kieserg A, Feldman R, Buchkremer G. Psychoeducational training for schizophrenic patients: background, procedure, and empirical findings. *Patient Educ Couns.* 1996;29:257–268.
83. Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res.* 2002;54:253–264.
84. Ito J, Oshima I. Distribution of EE and its relationship to relapse in Japan. *Int J Ment Health.* 1995;24:23–37.
85. Jarobe KS, Schartz SK. The relationship between medication noncompliance and cognitive function in patients with schizophrenia. *J Am Psychiatr Nurses Assoc.* 1999;5:S2–S8.
86. Jerrell JM. Cost-effectiveness of risperidone, olanzapine, and conventional antipsychotic medications. *Schizophr Bull.* 2002;28:589–605.
87. Jeste SD, Patterson TL, Palmer BW, Dolder CR, Goldman S, Jeste DV. Cognitive predictors of medication adherence among middle-aged and older outpatients with schizophrenia. *Schizophr Res.* 2003;63:49–58.
88. Joyce AT, Harrison DJ, Loebel AD, Ollendorf DA. Impact of atypical antipsychotics on outcomes of care in schizophrenia. *Am J Manag Care.* 2005;11(8suppl):S254–S261.
89. Kamali M, Kelly BD, Clarke M, et al. A prospective evaluation of adherence to medication in first episode schizophrenia. *Eur Psychiatry.* 2006;21:29–33.
90. Kamali M, Kelly L, Gervin M, Browne S, Larkin C, O' Callaghan E. Psychopharmacology: insight and comorbid substance misuse and medication compliance among patients with schizophrenia. *Psychiatr Serv.* 2001;52:161–166.
91. Kamali M, Kelly L, Gervin M, Browne S, Larkin C, O' Callaghan E. The prevalence of comorbid substance misuse and its influence on suicidal ideation among in-patients with schizophrenia. *Acta Psychiatr Scand.* 2000;101:452–456.
92. Kampman O, Kiviniemi P, Koivisto E, et al. Patient characteristics and diagnostic discrepancy in first-episode psychosis. *Compr Psychiatry.* 2004;45(3):213–218.
93. Kampman O, Laippala P, Vaananen J, et al. Indicators of medication compliance in first-episode psychosis. *Psychiatr Res.* 2002;110:39–48.
94. Kapur S, Ganguli R, Ulrich R, Raghu U. Use of random-sequence riboflavin as a marker of medication compliance in chronic schizophrenics. *Schizophr Res.* 1992;6:49–53.
95. Kashner TM, Rader LE, Rodell DE, Beck CM, Rodell LR, Muller K. Family characteristics, substance abuse, and hospitalization patterns of patients with schizophrenia. *Hosp Community Psychiatry.* 1991;42:195–196.
96. Kelly GR, Mamon JA, Scott JE. Utility of the health belief model in examining medication compliance among psychiatric outpatients. *Soc Sci Med.* 1987;25:1205–1211.
97. Kelly GR, Scott JE. Medication compliance and health education among outpatients with chronic mental disorders. *Med Care.* 1990;28:1181–1197.
98. Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomised controlled trial. *BMJ.* 1996;312:345–349.
99. Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomised controlled trial of compliance therapy. 18-month follow-up. *Br J Psychiatry.* 1998;172:413–419.
100. Kinon BJ, Hill AL, Liu H, Kollack-Walker S. Olanzapine orally disintegrating tablets in the treatment of acutely ill non-compliant patients with schizophrenia. *Int J Neuropsychopharmacol.* 2003;6:97–102.
101. Kiraly SJ, Gibson RE, Ancill RJ, Holliday SG. Risperidone: treatment response in adult and geriatric patients. *Int J Psychiatry Med.* 1998;28:255–263.
102. Klingberg S, Buchkremer G, Holle R, Monking HS, Hornung WP. Differential therapy effects of psychoeducational psychotherapy for schizophrenic patients: results of a 2-year follow-up. *Eur Arch Clin Neurosci.* 1999;249: 66–72.
103. Knapp M, King D, Pugner K, Lapuerta P. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. *Br J Psychiatry.* 2004;184:509–516.
104. Koukia E, Madianos MG. Is psychosocial rehabilitation of schizophrenic patients preventing family burden? a

comparative study. *J Psychiatr Ment Health Nurs.* 2005; 12(4):415–422.

105. Lecompte D, Pelc I. A cognitive-behavioral program to improve compliance with medication in patients with schizophrenia. *Int J Ment Health.* 1996;25:51–56.
106. Li Z, Arthur D. Family education for people with schizophrenia in Beijing, China: randomised controlled trial. *Br J Psychiatry.* 2005;187:339–345.
107. Lin IF, Spiga R, Fortsch W. Insight and adherence to medication in chronic schizophrenics. *J Clin Psychiatry.* 1979; 40:430–432.
108. Linn MW, Klett CJ, Caffey EM Jr. Relapse of psychiatric patients in foster care. *Am J Psychiatry.* 1982;139: 778–783.
109. Linden M, Godemann F, Gaebel W, et al. A prospective study of factors influencing adherence to a continuous neuroleptic treatment program in schizophrenia patients during 2 years. *Schizophr Bull.* 2001;27:585–596.
110. Lindstrom LH. A retrospective study on the long-term efficacy of clozapine in 96 schizophrenic and schizoaffective patients during a 13-year period. *Psychopharmacology.* 1989;99(suppl):S84–S86.
111. Linszen D, Lenior M, De Haan L, Dingemans P, Gersons B. Early intervention, untreated psychosis, and the course of early schizophrenia. *Br J Psychiatry Suppl.* 1998; 172(33):84–89.
112. Loffler W, Kilian R, Toumi M, Angermeyer MC. Schizophrenic patients' subjective reasons for compliance and noncompliance with neuroleptic treatment. *Pharmacopsychiatry.* 2003;36:105–112.
113. Macpherson R, Jerrom B, Hughes A. Drug refusal among schizophrenic patients treated in the community. *J Ment Health.* 1997;6:141–147.
114. Macpherson R, Jerrom B, Hughes A. A controlled study of education about drug treatment in schizophrenia. *Br J Psychiatry.* 1996;168:709–717.
115. Marom S, Munitz H, Jones PB, Weizman A, Hermesh H. Expressed emotion: relevance to rehospitalization in schizophrenia over 7 years. *Schizophr Bull.* 2005;31:751–758.
116. Marom S, Munitz H, Jones PB, Weizman A, Hermesh H. Familial expressed emotion: outcome and course of Israeli patients with schizophrenia. *Schizophr Bull.* 2002;28:731–743
117. Martic-Biocina S, Baric V. Factors important for compliance among Croatian patients suffering from schizophrenia: how to improve psychiatric services in Croatia? *Psychiatr Dan.* 2005;17:36–41.
118. McEvoy JP, Howe AC, Hogarty GE. Differences in the nature of relapse and subsequent inpatient course between medication-compliant and noncompliant schizophrenic patients. *J Nerv Ment Dis.* 1984;172:412–416.
119. McEvoy JP, Apperson LJ, Appelbaum PS, et al. Insight in schizophrenia: its relationship to acute psychopathology. *J Nerv Ment Dis.* 1989;177:43–47.
120. McFarlane WR, Lukens E, Link B, et al. Multiple-family groups and psychoeducation in the treatment of schizophrenia. *Arch Gen Psychiatry.* 1995;52:679–687.
121. Menzin J, Boulanger L, Friedman M, Mackell J, Lloyd JR. Treatment adherence associated with conventional and atypical antipsychotics in a large state Medicaid program. *Psychiatr Serv.* 2003;54:719–723.
122. Merinder LB, Viuff AG, Laugesen HD, Clemmensen K, Misfelt S, Espensen B. Patient and relative education in community psychiatry: a randomized controlled trial regarding its effectiveness. *Soc Psychiatry Psychiatr Epidemiol.* 1999;34:287–294.
123. Nageotte C, Sullivan G, Duan N, Camp PL. Medication compliance among the seriously mentally ill in a public mental health system. *Soc Psychiatry Psychiatr Epidemiol.* 1997; 32:49–56.
124. Nakonezny PA, Byerly MJ. Electronically monitored adherence in outpatients with schizophrenia or schizoaffective disorder: a comparison of first- vs. second-generation antipsychotics. *Schizophr Res.* 2006;82:107–114.
125. Nelson AA Jr, Gold BH, Hutchinson RA, Benezra E. Drug default among schizophrenic patients. *Am J Hosp Pharmacy.* 1975;32:1237–1242.
126. Ng RMK, Mui J, Chenung HK, Leung SP. Expressed emotion and relapse of schizophrenia in Hong Kong. *Hong Kong J Psychiatry.* 2001;11:4–11.
127. Norman RM, Malla AK. Examining adherence to medication and substance use as possible confounds of duration of untreated psychosis. *J Nerv Ment Dis.* 2002;190:331–334.
128. O'Donnell C, Donohoe G, Sharkey L, et al. Compliance therapy: a randomised controlled trial in schizophrenia. *BMJ.* 2003;327:834.
129. Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. *Psychiatr Serv.* 2000;51:216–222.
130. Olfson M, Mechanic D, Boyer CA, Hansell S. Linking inpatients with schizophrenia to outpatient care. *Psychiatr Serv.* 1998;49:911–917.
131. Owen RR, Fischer EP, Booth BM, Cuffel BJ. Medication noncompliance and substance abuse among patients with schizophrenia. *Psychiatr Serv.* 1996;47:853–858.
132. Parker G, Hadzi-Pavlovic D. The capacity of a measure of disability (the LSP) to predict hospital readmission in those with schizophrenia. *Psychol Med.* 1995;25:157–163.
133. Parkin DM, Henney CR, Quirk J, Crooks J. Deviation from prescribed drug treatment after discharge from hospital. *BMJ.* 1976;2:686–688.
134. Pristach CA, Smith CM. Medication compliance and substance abuse among schizophrenic patients. *Hosp Community Psychiatry.* 1990;41:1345–1348.
135. Pyne JM, Bean D, Sullivan G. Characteristics of patients with schizophrenia who do not believe they are mentally ill. *J Nerv Ment Dis.* 2001;189:146–153.
136. Razali MS, Hasanah CI, Che I, Khan UA, Subramaniam M. Psychosocial interventions for schizophrenia. *J Ment Health.* 2000;9:283–289.
137. Razali MS, Yahya H. Compliance with treatment in schizophrenia: a drug intervention program in a developing country. *Acta Psychiatr Scand.* 1995;91:331–335.
138. Rettenbacher MA, Hofer A, Eder U, et al. Compliance in schizophrenia: psychopathology, side effects, and patients' attitudes toward the illness and medication. *J Clin Psychiatry.* 2004;65:1211–1218.
139. Rijcken CA, Tobi H, Vergouwen AC, de Jong-van den Berg LT. Refill rate of antipsychotic drugs: an easy and inexpensive method to monitor patients' compliance by using computerised pharmacy data. *Pharmacoepidemiol Drug Safety.* 2004;13(6):365–370.
140. Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res.* 2002;57:209–219.

141. Rosa MA, Marcolin MA, Elkis H. Evaluation of the factors interfering with drug treatment compliance among Brazilian patients with schizophrenia. *Rev Bras Psiquiatria.* 2005; 27(3):178–184.
142. Rosenheck R, Chang S, Choe Y, et al. Medication continuation and compliance: a comparison of patients treated with clozapine and haloperidol. *J Clin Psychiatry.* 2000;61: 382–386.
143. Ruscher SM, De Wit R, Mazmanian D. Psychiatric patients' attitudes about medication and factors affecting noncompliance. *Psychiatr Serv.* 1997;48:82–85.
144. Rzewuska M. Drug maintenance treatment compliance and its correlation with the clinical picture and course of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2002; 26:811–814.
145. Sellwood W, Tarrier N. Demographic factors associated with extreme non-compliance in schizophrenia. *Soc Psychiatry Psychiatr Epidemiol.* 1994;29:172–177.
146. Sellwood W, Barrowclough C, Tarrier N, Quinn J, Mainwaring J, Lewis S. Needs-based cognitive-behavioral family intervention for carers of patients suffering from schizophrenia: 12-month follow-up. *Acta Psychiatr Scand.* 2001;104: 346–355.
147. Sellwood W, Tarrier N, Quinn J, Barrowclough C. The family and compliance in schizophrenia: the influence of clinical variables, relatives' knowledge, and expressed emotion. *Psychol Med.* 2003;33:91–96.
148. Seo MA, Min SK. Development of a structural model explaining medication compliance of persons with schizophrenia. *Yonsei Med J.* 2005;46(3):331–340.
149. Seltzer A, Roncari I, Garfinkel P. Effect of patient education on medication compliance. *Can J Psychiatry.* 1980;25: 638–645.
150. Serban G, Thomas A. Attitudes and behaviors of acute and chronic schizophrenic patients regarding ambulatory treatment. *Am J Psychiatry.* 1974;131:991–995.
151. Shvartsburd A, Sajadi C, Morton V, Mirabi M, Gordon J, Smith RC. Blood levels of haloperidol and thioridazine during maintenance neuroleptic treatment of schizophrenic outpatients. *J Clin Psychopharmacol.* 1984;4:194–198.
152. Sibitz I, Katschnig H, Goessler R, Unger A, Amering M. Pharmacophilia and pharmacophobia: determinants of patients' attitudes towards antipsychotic medication. *Pharmacopsychiatry.* 2005;38(3):107–112.
153. Smith CM, Barzman D, Pristach CA. Effect of patient and family insight on compliance of schizophrenic patients. *J Clin Pharmacol.* 1997;37:147–154.
154. Sullivan G, Wells KB, Morgenstern H, Leake B. Identifying modifiable risk factors for rehospitalization: a case-control study of seriously mentally ill persons in Mississippi. *Am J Psychiatry.* 1995;152:1749–1756.
155. Suzuki T, Uchida H, Takeuchi H, et al. Simplifying psychotropic medication regimen into a single night dosage and reducing the dose for patients with chronic schizophrenia. *Psychopharmacology.* 2005;181:566–575.
156. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatr Serv.* 2001;52:805–811.
157. Svedberg B, Mesterton A, Cullberg J. First-episode nonaffective psychosis in a total urban population: a 5-year follow-up. *Soc Psychiatry Psychiatr Epidemiol.* 2001;36: 332–337.
158. Swanson JW, Swartz MS, Elbogen EB. Effectiveness of atypical antipsychotic medications in reducing violent behavior among persons with schizophrenia in community-based treatment. *Schizophr Bull.* 2004;30:3–20.
159. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res.* 2000;42:241–247.
160. Trauer T, Sacks T. Mediation compliance: a comparison of the views of severely mentally ill clients in the community, their doctors, and their case managers. *J Ment Health.* 1998;7:621–629.
161. Valenstein M, Copeland LA, Owen R, Blow FC, Visnic S. Adherence assessments and the use of depot antipsychotics in patients with schizophrenia. *J Clin Psychiatry.* 2001;62:545–551.
162. Van Putten T, Crumpton E, Yale C. Drug refusal in schizophrenia and the wish to be crazy. *Arch Gen Psychiatry.* 1976;33:1443–1446.
163. Vaughan K, McConaghy N, Wolf C, Myhr C, Black T. Community treatment orders: relationship to clinical care, medication compliance, behavioral disturbance, and readmission. *Aust N Z J Psychiatry.* 2000;34:801–808.
164. Vauth R, Loschmann C, Rusch N, Corrigan PW. Understanding adherence to neuroleptic treatment in schizophrenia. *Psychiatry Res.* 2004;126:43–49.
165. Verghese A, John JK, Rajkumar S, Richard J, Sethi BB, Trivedi JK. Factors associated with the course and outcome of schizophrenia in India: results of a two-year multicentre follow-up study. *Br J Psychiatry.* 1989;154:499–503.
166. Weiden P, Rapkin B, Zygmunt A, Mott T, Goldman D, Frances A. Postdischarge medication compliance of inpatients converted from an oral to a depot neuroleptic regimen. *Psychiatr Serv.* 1995;46:1049–1054.
167. Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. *Schizophr Res.* 2004;66:51–57.
168. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv.* 2004;55: 886–891.
169. Weiss KA, Smith TE, Hull JW, Piper AC, Huppert JD. Predictors of risk of nonadherence in outpatients with schizophrenia and other psychotic disorders. *Schizophr Bull.* 2002;28:341–349.
170. Xiong W, Phillips MR, Hu X, et al. Family-based intervention for schizophrenic patients in China: a randomised controlled trial. *Br J Psychiatry.* 1994;165:239–247.
171. Yamada K, Watanabe K, Nemoto N, et al. Prediction of medication noncompliance in outpatients with schizophrenia: 2-year follow-up study. *Psychiatry Res.* 2006;141:61–69.
172. Yen CF, Chen CS, Ko CH, et al. Relationships between insight and medication adherence in outpatients with schizophrenia and bipolar disorder: prospective study. *Psychiatry Clin Neurosci.* 2005;59(4):403–409.
173. Ziguras SJ, Klimidis S, Lambert TJ, Jackson AC. Determinants of anti-psychotic medication compliance in a multicultural population. *Community Ment Health J.* 2001;37: 273–283.
174. Bendle S, Velligan DI, Mueller JL, Davis BV, Ritch JL, Miller AL. The Med-eMonitor[tm] for improving adherence to oral medication in schizophrenia. *Schizophr Bull.* 2005;31:519.