Eur Arch Psychiatry Clin Neurosci (2005) 255 : 143 – 148 DOI 10.1007/s00406-004-0547-5

ORIGINAL PAPER

M. Riedel · M. Strassnig · N. Müller · P. Zwack · H.-J. Möller

How representative of everyday clinical populations are schizophrenia patients enrolled in clinical trials?

Received: 16 April 2004 / Accepted: 3 September 2004 / Published online: 19 November 2004

Abstract *Introduction* There has been considerable discussion whether clinical trials accurately depict everyday practice. Restrictive inclusion/exclusion criteria, ethical considerations, differences in the severity of psychopathology between clinical and trial patients, or safety issues may bias results, which in turn may rather represent outcome for the "ideal" than for the "average" patient. Therefore, translation into psychiatric practice may be difficult. *Methods* A retrospective case-control study was performed. Schizophrenia inpatients at the LMU Department of Psychiatry, Munich, Germany, who had participated in clinical trials were compared to regular patients serving as controls. Probands and controls were matched by DSM-IV diagnosis, gender and age. The AMDP module, CGI and GAF were used to compare psychopathology. In addition, charts were reviewed for medication dosages, concurrent medical and neurological illness, and clinical history such as age of onset or family history. *Results* A total of 200 probands (100/100) were enrolled in the study. With respect to psychopathology, formally thought disordered or suicidal patients were significantly less likely to be study participants ($n = 3$) than controls ($n = 22$; $p \leq 0.05$). Similarly, negative schizophrenia symptoms were significantly less often present in study participants ($n = 17$) than in controls ($n = 38$; $p \leq 0.05$). Study participants were also medically and neurologically healthier than controls. ($p = 0.05$ respectively). No differences in overall illness severity as depicted by CGI and GAF were observed. *Conclusion* We found the patients included in our clinical trials representative of the patient encountered in routine clinical practice. Adherence to inclusion and exclusion criteria prevents inclusion of severely ill (e. g. suicidal) patients requiring a more intensive treatment setting. Illness severity was found to be similar in trial participants and controls, and indicates an overall comparably severe psychopathology. The more chronic, rather treatment refractory patients were also not reflected in the trial participant pool; this population may arguably not represent the average clinical patient either. A more careful administration of antipsychotic medication was found in trial participants and may effectively be considered "good clinical practice".

Key words schizophrenia · clinical trials · AMDP · antipsychotics · psychopathology · comorbidities

M. Riedel, MD (✉) · M. Strassnig · N. Müller · P. Zwack · H.-J. Möller
Ludwig-Maximilians-University Munich
Dept. of Psychiatry and Psychotherapy
Nußbaumstraße 7
80336 Munich, Germany
Tel.: +49-89/5160-5755
Fax: +49-89/5160-5188
E-Mail: Riedel@psy.med.uni-muenchen.de

Introduction

Pharmaceutical drug companies tend to maximize the likelihood that a clinical trial will detect an effect of an investigative drug, if one exists (Leber and Davis 1998). As a result, restrictive exclusion and inclusion criteria are introduced and may interfere with generalizability of trial results. Related difficulties involved in the recruitment process are well known to researchers. Eventually, only 10 to 15 % of patients admitted to the average psychiatric hospital are eligible for a clinical trial and can be included (Hofer et al. 2000). The question arises, whether we are missing a large portion of "everyday patients" when imposing such criteria.

Schizophrenia is a chronic illness and poses considerable health risks onto the patient (Brown et al. 1999). Psychiatric comorbidities such as substance abuse or depression, or general medical problems including obesity, insulin resistance and high blood pressure are frequently present in schizophrenia patients (Goldman 1999) and complicate treatment. Despite proper treatment, a large portion of patients may chronically suffer from schizophrenic symptoms, or even be considered medication refractory (Hellewell 1999). In fact, many schizophrenia patients are multi-morbid (Jeste et al.

1996) and thus, receive pharmacological treatment for a variety of medical problems in addition to psychotropic medication. Such a pattern may rather represent the rule than the exception.

The ability to consent to a clinical trial per se implies a rather healthy patient with respect to psychopathology. More readily accessible information for patients about their illness, clinical trials or treatment options in general demands increasingly comprehensive informed consent procedures, which in turn requires healthier patients to comprehend the provided information. In this respect, severely ill or unstable patients, such as suicidal or thought disordered patients; or patients admitted to locked units, are usually excluded from clinical trials.

Phase III clinical trials are mandatory to gain market approval for the tested drug. However, due to the mentioned flaws it is frequently argued that Phase III trials do not reflect everyday clinical practice (Keith 2001). As a consequence, about 80% of the "target population" may receive medication which has never been tested on them. Regular patients may be different from study subjects under a variety of aspects. They may be more severely ill and require a variety of related and unrelated comedications for their psychiatric illness, making them more prone to experience adverse drug interactions. Yet, risks associated with polypharmacy are usually not addressed in clinical trials.

Therapeutic strategies in phase III trials are usually characterized by strict protocols, restrictive use of comedications, and close clinical patient monitoring. While the patient may actually receive more attention, investigators may often be hesitant when it comes to changing ineffective trial medications to more promising alternatives. Thus, treatment modalities used in clinical trials may be unrepresentative of practices in the actual clinical encounter.

We hypothesize that investigative clinical drug research does not necessarily translate into clinical care. The patient population included in clinical trials may differ from the "average patient" seen in clinical practice with respect to several parameters such as the severity of psychopathology, chronicity of illness, general medical health. They may also receive treatment different from everyday practice routine. In order to assess these differences, we retrospectively compared patients enrolled in clinical trials with regular patients matched by diagnosis, gender and age.

Methods

A retrospective case-control study was conducted. Study subjects were recruited according to DSM-IV diagnosis of schizophrenia (295.x). All participants were inpatients at the Ludwig Maximilians University Munich, Department of Psychiatry from 1995 to 1999. The Department of Psychiatry is not only a research hospital, but also serves as a primary referral center for patients from the city of Munich and other parts of Bavaria. Thus, a priori selection bias does not apply. To be eligible for analysis, study subjects had to be participants in various phase III clinical trials with neuroleptics conducted between 1995 and 1999. Trials included comparisons of various neuroleptics such as ziprasidone vs. haloperidol, olanzapine vs. clozapine, olanzapine vs. haloperidol, haloperidol vs. risperidone, or iloperidone vs. haloperidol. Patients were enrolled in our analysis on a consecutive basis. Initial cut-off point was enrollment in a clinical trial on Jan 1, 1995. All patients subsequently enrolled in clinical trials were considered for inclusion in our retrospective analysis. The last subject (n = 100) used for our analysis was enrolled in a clinical trial in 1999. A control group matched for diagnosis, gender and age was included as well. As for control selection, the appropriate patient admitted closest to the admission date of the trial participant was selected. Primary match variable was diagnosis.

Demographic and clinical history data are reliably documented in patient charts. Standard lab analyses, electrocardiogram (ECG) and electroencephalogram (EEG) are performed routinely during every admission process. ECG abnormalities as well as medical comedication on admission were included in the analysis and termed "internistic problems"; similarly, documented seizure disorders and EEG abnormalities such as slow wave complexes, and symptoms of tardive dyskinesia resulting from long-term neuroleptic medication including puckering and pursing, rapid eye blinking, rapid movements of the arms, legs, and trunk, or slow-amplitude tremors were characterized as "neurologic problems" and incorporated as such in the analyses.

The psychopathological measures examined encompassed: clinical global impression (CGI) and Clinical Global Impression of improvement (CGI-I; Guy 1976); AMDP module and global assessment of functioning scale (GAF; Endicott et al. 1976). The AMDP module is an operationalized documentation system for psychopathology, and was developed by a German-Swiss-Austrian "Association for Methodology and Documentation in Psychiatry" (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie, 1981; Guy and Ban 1982). Reliability and validity have been established (Bobon et al. 1983; Renfordt et al. 1983). AMDP sheets are checklists with 151 different items of psychopathology; the items are derived from the original description of symptoms by Kraepelin (Heimann H 1983). Items are graded from 0 to 5 according to severity of symptoms. Factor analysis (Gebhardt et al. 1983) leads to 8 distinct psychopathological syndromes or clusters, derived from 84 of the items: paranoid-hallucinatory, depressive, psychoorganic, manic, hostile, vegetative, apathic and obsessive compulsive syndrome. In addition, a negative syndrome was extracted by Angst et al. (1989). Together, the 9 clusters accurately depict psychopathology. The single AMDP items "suicidality" and "formal thought disorder" on admission were also incorporated in the statistical analysis; both served as additional measures for the ability to consent to a research protocol. Suicidality at admission was defined as a score of higher than 1. Accordingly, the presence of formal thought disorder at admission was defined as a score of higher than 1. AMDP checklists, CGI, and GAF are routinely completed twice one to four days after inpatient admission and on the day of discharge for every patient; both time points were used for analysis, respectively.

For easier comparability, neuroleptic treatments were recalculated into chlorpromazine-equivalents according to Jahn and Mussgay (1989) and where appropriate for atypical medication, according to Benkert and Hippius (1996). In addition, biographic information including education, marital status and living arrangements; and clinical history including age of onset, age at first hospitalization, first degree family history of schizophrenia, overall duration of illness, number of inpatient stays and ECT history were reviewed. Duration of illness was calculated from the date of the first inpatient admission until enrollment in the pertinent clinical trial or matched inpatient admission respectively. In case of a medication switch, cut-off day for analysis was the first day of introduction of the new medication.

SPSS (for windows) software was employed for data analysis. Descriptive analysis including mean, range and standard deviation for continuous variables was carried out to determine whether the variable(s) is (are) normally distributed and frequency counts for categorical data (for example gender, race, etc.) were done to examine the proportions of various socio-demographic characteristics. Resulting values were examined for the whole group and for the patient sample versus healthy controls. Student t-tests and Chi-Square tests were employed to look for statistical differences between the means of two or more variables.

Results

Two hundred subjects were included in the analysis: 106 were male, 94 female. One hundred of the subjects had been enrolled in clinical phase III trials; 100 controls were matched according to age, gender and DSM-IV diagnosis.

Table 1 shows demographic and clinical data. Enrolled females (n = 94; age 44.4 ± 12.2 years) were older than males (n = 106; age 33 ± 10.1 years; $p \leq 0.05$). Correspondingly, age of females at the first inpatient admission (34.9 ± 8.3 years) was significantly higher than the age of males (27.5 ± 9.8 years; $p \leq 0.05$). Both study groups were homogenous with regard to other demographic variables (education level, marital status, living arrangements).

Twenty six patients carried a diagnosis of disorganized schizophrenia (DSM-IV 295.1; 13 study participants/13 controls), 9 had a diagnosis of catatonic schizophrenia (295.2; 3/6), 129 were classified as paranoid schizophrenics (295.3; 67/62), 6 suffered from schizophreniform disorder (295.4; 4/2), 5 had residual type schizophrenia (295.6; 2/3), 21 schizoaffective disorder (295.7; 9/12), 3 were diagnosed with brief psychotic disorder (298.8; 3/0), 2 had undifferentiated schizophrenia

Table 1 Demographics, history and clinical characteristics of study participants versus matched controls

Characteristics	Study participants N = 100	Controls N = 100	Significance
Demographics			
Gender (Male/Female)	54/46	52/48	
Age	37.5 (±11.4)	41.1 (±13.1)	$p \leq 0.05$
Education			
No degree	17	19	ns[1]
High school	47	41	ns
GED equivalent	17	13	ns
At least some college	19	26	ns
Marital status			
Married, together	22	23	ns
Single	62	62	ns
Other (separated, widowed)	16	15	ns
Living arrangements			
Independent	93	94	ns
Supervised	6	5	ns
Homeless	1	1	ns
Clinical history			
Age of onset	27.4 (±8.6)	28.0 (±10.6)	ns
Age at first hospitalization	30.3 (±9.5)	31.8 (±12.2)	ns
Family history of psychosis[2]	33	30	ns
Duration of illness in months	93 (±103.8)	133 (±113)	$p \leq 0.05$
Previous hospitalizations	1.37 (±1.8)	3.55 (±3.8)	$p \leq 0.001$
ECT treatment	1	5	ns
Clinical status/baseline			
Lab abnormalities	34	40	ns
Internistic comorbidities	2	12	$p \leq 0.05$
Internistic comedication	19	35	$p \leq 0.05$
Neurologic comorbidities	17	25	$P \leq 0.05$
Medication on discharge			
Typical antipsychotic	18	37	$p \leq 0.05$
Atypical neuroleptics	73	45	$p \leq 0.05$
Combinations	1	9	$p \leq 0.05$
No medication	8	9	ns
Treatment success CGI-I			
No change	8	18	ns
Minimal improvement	28	22	ns
Much improved	35	36	ns
Very much improved	29	24	ns

[1] *ns* not significant; [2] First degree relatives, positive/negative history

(295.9; 1/1), and 2 were diagnosed with psychotic disorder NOS (298.9; 1/1).

Looking at the clinical psychiatric history, study participants had significantly shorter duration of illness (93 ± 103.8 months) than controls (133 ± 113 months $p \leq 0.05$) and significantly lower numbers of psychiatric hospitalizations (n = 1.37 ± 1.8 vs. n = 3.55 ± 3.8; $p \leq 0.001$). They also were less likely to suffer from internistic comorbidities (n = 2 vs. n = 12; $p \leq 0.05$) or neurologic abnormalities (n = 17 vs. n = 22; $p \leq 0.05$) than controls and were prescribed fewer internistic comedications (n = 19 vs. n = 35; $p \leq 0.05$). In both groups, there were participants with a history of Electroconvulsive Therapy (n = 1 study participant vs. n = 5 controls) or were previously treated with depot antipsychotics (n = 9 vs. n = 13), yet no statistically significant differences were observed for these variables.

Table 2 depicts the clinical course and psychopathology scores of study patients versus controls. Average treatment duration in the various trials was 31.6 (± 22.4) days. There were no differences in illness severity as defined by CGI and GAF admission and discharge scores between study subjects and controls. With respect to AMDP psychopathology, study subjects were more likely to show symptoms of the AMDP paranoia cluster characterized by delusions and hallucinations; there was also a trend for study subjects to suffer from more severe symptoms of the apathia cluster with affective blunting, slowness and circumstantiality. In contrast, study subjects were less likely to present with symptoms of the AMDP mania cluster. There was also a trend towards significancy for study subjects to be less hostile (e. g. aggressive, dysphoric, with poor insight) than controls.

When looking at the single AMDP items suicidality and formal thought disorder on admission, formally thought disordered or suicidal patients were significantly more likely to be controls (n = 22; n = 4) than study participants (n = 3; n = 0; $p \leq 0.05$ respectively). Similarly, negative schizophrenia symptoms were significantly more often present in controls (n = 38) than in study participants (n = 17; $p \leq 0.05$).

Study subjects were less likely to be discharged on classic antipsychotics (n = 18 vs. n = 37; $p \leq 0.05$), and conversely more likely to be discharged on atypical neuroleptics (n = 73 vs. n = 45; $p \leq 0.05$) than controls. One study participant and 9 controls required antipsychotic combination therapy on discharge ($p \leq 0.05$).

Discussion

We attempted to address in our analysis two major points: (1) Whether the patient population included in clinical trials reflects the pattern of "average patients" observed in clinical practice, and (2) whether treatment modalities in clinical trials differed from those in a naturalistic setting.

With respect to the first question, we did find important differences between study subjects and controls in several ways. Study subjects were characterized by substantially shorter durations of illness and fewer psychiatric hospitalizations, indicating that they were the less chronically ill in terms of illness course. In addition, laboratory abnormalities, general medical and neurological comorbidities were present more often in controls than in study participants. Thus, the health status was better in the study population. A corresponding pattern has been consistently reported in the literature (Robinson et al. 1996; Arnold et al. 1997). Finally, study participants were numerically less likely to have had ECT and depot-neuroleptic medication, although these differences did not reach statistical significance.

Table 2 Clinical course of study participants vs. controls

Characteristics	Admission		Discharge	
	Participants	Controls	Participants	Controls
GAF	41.7 (±14.2)	42.5 (±16.4)	62.4 (±14.9)	60.2 (±17.7)
CGI	5.9 (±0.9)	6.1 (±0.8)	4.4 (±1)	4.6 (±1)
CPZ-units[1]	219.0 (±194.6)	290.0 (±484.1)	293.0 (±206.4)	329.0 (±232.5)
AMDP Psychopathology				
Syndromes				
Paranoid-hallucinatory	0.69 (±0.62)*	0.47 (±0.26)	0.07 (±0.3)	0.08 (±0.34)
Depressive	0.33 (±0.51)	0.34 (±0.5)	0.03 (±0.2)	0.03 (±0.2)
Psychoorganic	0.16 (±0.4)	0.19 (±0.1)	0.01 (±0.4)	0.04 (±0.01)
Manic	0.1 (±0.3)**	0.27 (±0.6)	0.02 (±0.1)	0.06 (±0.2)
Hostile	0.35 (±0.6)[2]	0.53 (±0.08)	0.09 (±0.04)	0.02 (±0.5)
Vegetative	0.04 (±0.2)*	0.00 (±0)	0.00 (±0)	0.00 (±0)
Apathic	0.96 (±0.7)[2]	0.78 (±0.6)	0.3 (±0.5)	0.26 (±0.5)
Negative	0.68 (±0.6)	0.62 (±0.5)	0.11 (±0.3)	0.16 (±0.4)
Obsessive compulsive	0.06 (±0.3)	0.11 (±0.4)	0.04 (±0.2)	0.03 (±0.2)

[1] Chlorpromazine Equivalents; [2] Trend towards Significancy ($p = 0.68$)
* $p \leq 0.05$; ** $p \leq 0.005$

When looking at psychopathology, study subjects were more likely to show symptoms of the AMDP paranoia cluster characterized by delusions and hallucinations and of the apathia cluster with affective blunting, slowing of thoughts and circumstantiality. In contrast, study subjects were less likely to be hostile (e. g. less aggressive, dysphoric, no insight) and manic than controls.

The single AMDP items suicidality and thought disorder were significantly less often present in study subjects than in controls. Inclusion of suicidal patients into clinical trials merits no consideration, since the ethical implications seem clear; thought disordered patients do not always fulfill criteria to give *informed* consent to a clinical investigation. In this respect, thorough adherence to trial inclusion/exclusion criteria may skew generalizability of results, but may actually bias results in the proper direction: these acutely ill patients usually require emergency medication and often extensive supervision in closed units, which may not be always available in clinical settings and thus not reflect "normal clinical practice" anyway.

Importantly, whereas AMDP psychopathology cluster differences were found, we observed no differences in illness severity as defined by CGI or GAF scores on admission between study participants and controls. The groups also did not differ significantly in terms of demographic variables, a pattern, which has been found before (Keith et al. 2001); in these respects, clinical trial results may well be generalizable. Considering the longer duration of illness and a higher number of previous hospitalizations, slightly more negative symptoms, quantitatively more CPZ units on admission and a higher proportion of ECT as well as depot-neuroleptic treatments in controls, these patients may represent a more treatment-refractory subgroup of schizophrenia patients. Patients alike may be encountered predominantly in longer-term facilities (Fisher et al. 2001), or high-level care institutions such as university clinics; if they necessarily represent the "average patient" either may remain in question.

As an interesting connotation, patients who participate in our clinical trials do not receive any financial compensation; therefore economic considerations do not apply when choosing to participate in a research study. Therefore, a financial bias is not introduced a priori through patients' respective considerations.

To the second question, we also found some differences in treatment modalities. Controls were treated with more CPZ units than study participants throughout the inpatient stay, although the differences did not reach statistical significance. Their medication was also more readily switched in the course of treatment. When looking at treatment results in terms of CGI and GAF discharge scores, no differences were observed between groups.

This pattern may be interpreted in terms of more restrictive treatment plans of clinical trials, as investigators may be cautious to prematurely switch from study medications to alternatives. It seems that trial subjects have more time to improve their psychopathology. They are frequently observed more thoroughly (provided the frequent formalized assessments required in clinical trials), and tolerance towards delayed treatment responses may have been higher on the side of the investigator, especially when considering the lower quantities (depicted by a slightly lower amount of CPZ units) of antipsychotic medication administered. Still, since the outcome regarding psychopathology and illness severity was not different between groups, patients enrolled in a clinical study may even benefit from such a lower dose of antipsychotics dispensed. In fact, the higher dose of psychotropic medications together with more frequent medication switches in controls may point to a higher incidence of drug related side-effects. This may be especially important with regard to the observed higher neurologic comorbidity rates in controls, since in this respect they may be more prone to side-effects (Van Os et al. 1997. The smaller doses of antipsychotics dispensed to clinical trial participants might in fact be beneficial to the average patient in terms of a lower risk of side effects (Wirshing et al. 2003) and contribute to medication compliance (Perkins 2002). Interestingly, in cases of insufficient medication efficacy, study participants were more likely to be discharged with atypical antipsychotic medication. Given the likelihood of better long-term compliance (Nasrallah and Mulvihill 2001) associated with atypical antipsychotic medication, this pattern merits further investigation.

In conclusion, we found that the patients included in clinical trials are representative of the average patient encountered in routine clinical practice. Indeed, thorough adherence to inclusion/exclusion criteria may prevent the inclusion of severely ill (e. g. suicidal) patients requiring a more intensive treatment setting. Illness severity was similar in trial participants and controls and indicates an overall comparable psychopathology. The more chronic, treatment refractory patients and patients with schizophrenic negative symptoms were also not reflected in the trial participant population; this population may arguably not represent the average clinical patient either. Last but not least, the administration of lower doses of antipsychotic medication in clinical trials with comparable psychopathology improvement to control subjects may effectively be considered "good clinical practice" and certainly warrants application in usual clinical settings.

However, we must not forget that many clinical trials still offer results on treatment efficacy under best-practice conditions (Wells 1999). Thus, cautious administration of new drugs is warranted and critical clinical judgement is still standard of care. On the other hand, clinical trials are necessary to investigate new treatment options and ethical considerations have to be taken into account here also, if from a different perspective: There are many common clinical situations, when people require treatment and there is clear experimental evidence available to indicate what the clinician should do, but that treatment is not provided (Frank et al. 2002).

Clearly, research fails to improve clinical care unless research results become part of routine practice.

The results of our study are limited in several ways. The data were obtained retrospectively, while a prospective approach might have been required for better generalizability. Yet, the methodological approach to such a prospective study design would be complicated, and recruitment of a substantial patient sample might prove difficult. Second, we looked at data of inpatients; therefore the results may not directly be applicable to ambulatory research. Certainly, however, data are applicable for a regular hospital setting.

References

1. AMDP (1981) Das AMDP-System. Manual zur Dokumentation psychiatrischer Befunde. Berlin – Heidelberg – New York: Springer
2. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, American Psychiatric Association
3. Angst J, Scharfetter C, Stassen HH (1989) Classification of schizo-affective patients by multidimensional scaling and cluster analysis. Psychiatr Clin 16:254–264
4. Arnold LE, Hoagwood K, Jensen PS, Vitiello B (1997) Toward clinically relevant clinical trials. Psychopharmacol Bull 33(1): 135–142
5. Benkert O, Hippius H (1996) Psychiatric Pharmacotherapy. 6th edition. Berlin – Heidelberg – New York – Tokyo, Springer, pp 226–277
6. Bobon D, Baumann U, Angst J, Helmchen H, Hippius H (eds) (1983) The AMDP-system in pharmacopsychiatry. Basel: Karger
7. Brown S, Birthwistle J, Roe L, Thompson C (1999) The unhealthy lifestyle of people with schizophrenia. Psychol Med 29(3): 697–701
8. Endicott J, Spitzer RL, Fleiss JL, Cohen J (1976) The Global Assessment Scale – a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 33:766–771
9. Fisher WH, Barreira PJ, Geller JL, White AW, Lincoln AK, Sudders M (2001) Long-stay patients in state psychiatric hospitals at the end of the century. Psychiatr Serv 52(8):1051–1056
10. Frank E, Rush AJ, Blehar M, Essock S, Hargreaves W, Hogan M, et al. (2002) Skating to where the puck is going to be: a plan for clinical trials and translation research in mood disorders. Biol Psychiatry 52:631–654
11. Gebhardt R, Pietzcker A, Strauss A, Stoeckel M, Langer C, Freudenthal A (1983) Skalenbildung im AMDP-System. Arch Psychiatr Nervenkr 233:223–245
12. Goldman LS (1999) Medical illness in patients with schizophrenia. J Clin Psychiatry (Suppl 21):10–15
13. Guy GW, Ban TA (1982) The AMDP system. Manual for the assessment and documentation of psychopathology. Berlin – Heidelberg – New York: Springer
14. Guy W (1976) ECDEU Assessment manual for psychopharmacology. US Dept of Health and Human Services publication ADM 76(338), pp 524–535
15. Heimann H (1983) From Kraepelin to the system of the Association for Methodology and Documentation in Psychiatry. Acta Psychiatr Belg 83(2):147–154
16. Hellewell JS (1999) Treatment-resistant schizophrenia: reviewing the options and identifying the way forward. J Clin Psychiatry 60(Suppl 23):14–19
17. Hofer A, Hummer M, Huber R, Kurz M, Walch T, Fleischhacker WW (2000) Selection Bias in Clinical Trials With Antipsychotics. J Clin Psychopharmacol 20:699–702
18. Jahn T, Mussgay L (1989) Die stationäre Kontrolle möglicher Medikamenteneinflüsse in experimental-psychologischen Schizophreniestudien: Ein Vorschlag zur Berechnung von Chlorpromazin-Äquivalenten. Zeitsch Klein Psychologie 3:257–267
19. Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP (1996) Medical comorbidity in schizophrenia. Schiz Bull 22(3):413–430
20. Leber PD, Davis CS (1998) Threats to the Validity of Clinical Trials Employing enrichment strategies for sample selection. Controlled Clinical Trials 19:178–187
21. Keith SJ (2001) Evaluating characteristics of patient selection and dropout rates. J Clin Psychiatry 62(Suppl 9):11–14
22. Nasrallah HA, Mulvihill T (2001) Iatrogenic disorders associated with conventional vs. atypical antipsychotics. Ann Clin Psychiatry 13(4):215–227
23. Perkins DO (2002) Predictors of non-compliance in patients with schizophrenia. J Clin Psychiatry 63(12):1121–1128
24. Renfordt E, Busch H, v Cranach M, Gulbinat W, Tegeler J (1983) Particular aspects of the interrater reliability of the AMDP psychopathology scale. In: Bobon D, Baumann U, Angst J, Helmchen H, Hippius H (eds) AMDP-system in pharmacopsychiatry. Modern problems of pharmacopsychiatry 20. Basel: Karger, pp 119–124
25. Robinson D, Woerner MG, Pollack S, Lerner G (1996) Subject selection Biases in Clinical Trials: Data From a Multicenter Schizophrenia Treatment Study. J Clin Psychopharmacol 16:170–176
26. Van Os J, Fahy T, Jones P, Harvey I, Toone B, Murray R (1997) Tardive Dyskinesia: who is at risk? Acta Psychiatr Scand 96(3): 206–216
27. Wells KB (1999) Treatment Research at the Crossroads: The Scientific Interface of Clinical Trials and Effectiveness Research. Am J Psychiatry 156:5–10
28. Wirshing DA, Pierre JM, Erhart SM, Boyd JA (2003) Understanding the new and evolving profile of adverse drug effects in schizophrenia. Psychiatr Clin North Am 26(1):165–190