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ORIGINAL PAPER

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German research network on schizophrenia

Bridging the gap between research and care

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Abstract *The German Research Network on Schizophrenia* (GRNS) is a nationwide network of presently 16 psychiatric university departments, 14 state and district hospitals, as well as six local networks of psychiatric practices and general practitioners, which are collaborating in about 25 interrelated, multicentre projects on schizophrenia research. The GRNS aims to intensify collaboration and knowledge exchange between leading research institutions and qualified routine care facilities, both within (horizontal network) and between (vertical network) the two levels of research and care, in order to create the scientific preconditions for optimization of care in patients with schizophrenia. With respect to illness development, the network is organized into two main "Project Networks" (PN). Whereas PN I targets the implementation of early detection and early intervention strategies, PN II aims at optimization of acute and long-term treatment, especially in first-episode patients. PN II also includes projects aiming at improvement of rehabilitation, particularly in patients with residual symptoms. Furthermore, there is a "Special Network" on molecular and pharmaco-genetics. Several more general projects address fighting stigma and discrimination, health care economy, continuing medical education, quality assurance, and methodology. The network is mainly funded by the German Ministry for Research spanning a period of 5 years.

Key words schizophrenia · early intervention · long-term treatment · quality assurance · genetics

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Background and aims

The complexity of psychiatric disorders on the one hand and the progressive specialization in research especially when using complex biological methods on the other hand results in an increasing necessity for inter- and intra-disciplinary collaboration organized in larger networks. Primarily, such a strategy seems promising to find answers to the urging and complex questions still unresolved.

The *German Research Network on Schizophrenia* (GRNS) is one of meanwhile 14 medical research networks funded by the German Federal Ministry of Education and Research (BMBF) in order to improve care in patients with illnesses characterized by high morbidity and/or mortality. Each of these networks is funded with up to 2.5 million Euro/year for up to 5 years. Bringing together the leading research institutions with qualified routine care facilities, the GRNS will, in the long run, optimize preventive strategies, acute and long-term treatment, and rehabilitation of patients with schizophrenia by means of an intensified

collaboration and knowledge exchange within (horizontal networking) and between (vertical networking) the two levels of research and care. The motivation to establish such a network for schizophrenia originates from imperfections of the actual situation. On the one hand, coordination of psychiatric services is insufficient and needs to be optimized and on the other hand, research does not tap its full potential on account of a separation of research and mental healthcare institutions due to historic reasons. This leads to an insufficient transfer of new knowledge from research to practice and insufficient recognition of problems in everyday care worth being scientifically investigated.

Thus, the major objective of the GRNS is to create the scientific preconditions for the implementation of preventive strategies and for the optimization of treatment and rehabilitation in order to allow for an improvement of the course and the outcome of the illness along with considering cost-benefit aspects. The related structural goal – in a way to be taken as a precondition – consists in the establishment of long-term communication structures between research, service, consumers and the public. A means for attaining these aims is the creation or expansion, intensified utilization and routine application of cooperation between research and healthcare institutions. With regard to the funding by the Federal Ministry of Research (and not the Ministry of Health), the framework for attaining these objectives is made up of research projects, which constitute the means or at least create the preconditions for intensified collaboration between institutions and optimized care for patients with schizophrenia.

Organization

Against this background, the GRNS has been designed as a network of about 25 interrelated research studies and projects on healthcare education with high practice relevance.

The GRNS is organized into two main "Project Networks" (PN) with respect to illness development. PN I focuses primarily on detection, recognition and early intervention in the prodromal and mounting psychotic stage of the first episode. Based on a newly developed two-step early recognition inventory, psychological and pharmacological treatment strategies for prevention of first episodes are evaluated in identified high-risk persons. PN II is subdivided into three subnetworks (SN) targeting the three phases after manifestation of the illness, i. e. acute treatment (SN1), long-term treatment (SN2) and rehabilitation (SN3). Particular emphasis is put on optimization of the treatment of first-episode patients and on rehabilitation in patients with residual symptoms. Furthermore, prodromal symptoms as predictors of reexacerbation, probably permitting relapse prevention by early intervention, are investigated. In addition, targeted rehabilitation programmes should improve recovery and prevent long-term morbidity. Quality of care in hospitals and practices is evaluated and improved by quality assurance programmes implementing guidelines for out- and inpatient treatment.

Basic research on structural and functional brain imaging and genetic markers investigates underlying determinants of the manifestation and re-manifestation of the illness as well as the individual response to drug treatment. The latter research is bundled in a "Special Network" on molecular and pharmaco-genetics. A number of more general projects on fighting stigma and discrimination (Gaebel et al. 2002a), healthcare economy, postgraduate training, quality assurance, and methodology complete the more care-related spectrum of network projects (Fig. 1; see homepage www.kompetenznetz-schizophrenie.de for more information).

Generally, the studies are designed in such a manner, that vertical and horizontal networking is forced, essential or at least supported. In order to create synergy and added value as important criteria for successful networking, most of the projects are strongly interrelated regarding conceptual background, methods and organization. For instance, the various studies use the same, standardized instruments for assessing clinical and neuropsychological status to allow cross-referencing between the studies. A total of presently 16 psychiatric university departments, 14 state and district hospitals, as well as six local networks of psychiatric practices and general practitioners throughout Germany participate in the network. Almost all projects are multicentre studies with up to 13 participating hospitals or up to 55 participating private practices, respectively. Several centres participate – partly as leading centre, partly as study centre – in more than one study. This cross-linking of centres and projects has several advantages: (1) it allows to transfer patients from early intervention to first-episode studies (or from acute to long-term treatment or inpatient to outpatient studies) within the same institution or city when the illness proceeds; (2) it facilitates funding of personnel which can be shared by different projects in the same institution; and (3) it creates mutual obligations between institutions, which helps to keep enrolment of patients in these centres high and helps to create the essential "spirit" of networking. Thus, this cross-linking of several, tuned multi-centre studies creates a horizontal network in form and content.

Beyond horizontal networking, especially the early recognition, quality assurance and fighting stigma and discrimination projects are very conducive to vertical networking. For instance, projects on early recognition of schizophrenia are only possible on the basis of an intensive collaboration of specialized research centres, which develop and use valid instruments for detection, with multiple care institutions, which transfer risk persons to such specialized diagnostic centres.

The coordination of the GRNS (Fig. 2) is primarily held by the *Executive Committee* together with the *Head Office,* which is located at the Department of Psychiatry in Düsseldorf. Whereas the head office takes the more administrative coordination, the executive committee is

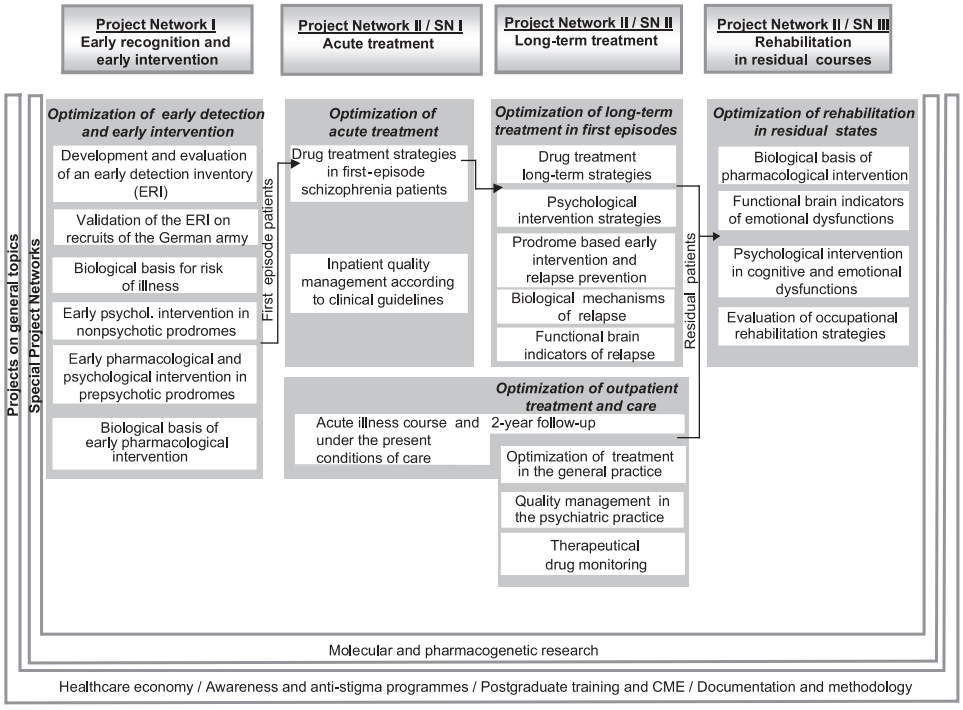

Fig. 1 Projects of the German Research Network on Schizophrenia with the various Project Networks (PN) and Subnetworks (SN)

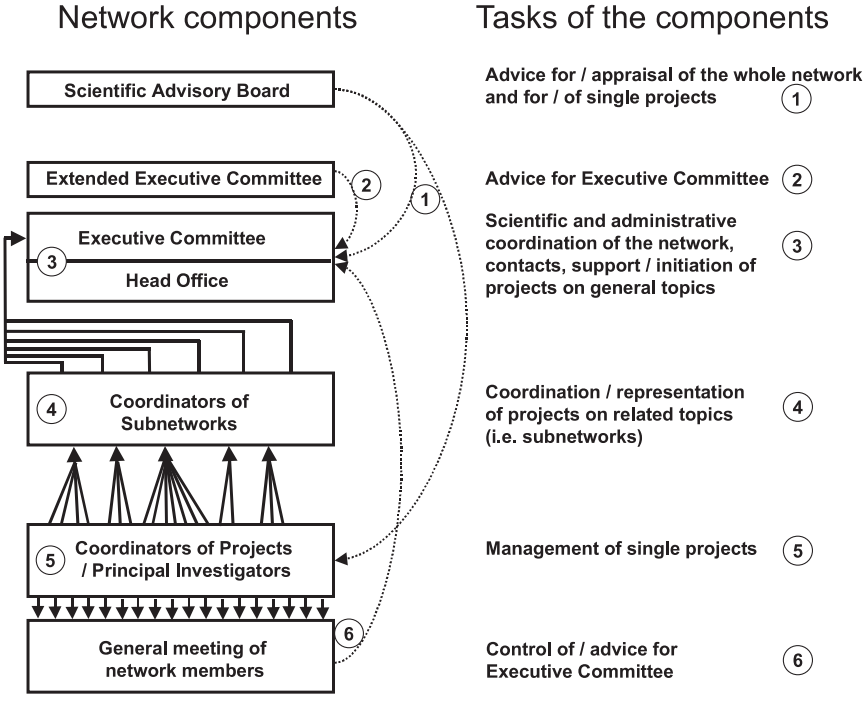

Fig. 2 Organization of the German Research Network on Schizophrenia

responsible for the scientific coordination and future development of the network. Besides the six coordinators of the project networks, subnetworks and the special network on molecular and pharmaco-genetics as regular members of the executive committee (i. e. authors GB, HH, JK, WM, HJM, WG), the director of the head office (author WW), as well as one representative of the association of the psychiatric state hospitals, the psychiatrists in practices, and the relatives, respectively, and a schizophrenia patient are consulting members of the executive committee. The main initiators and applicants and now the speakers of the network are W. Gaebel (Speaker, Düsseldorf) and H.-J. Möller (Vice-Speaker, Munich). Further advice for the executive committee on the one hand comes from a *Scientific Advisory Board* with nine international experts, which additionally functions as a review committee for the funding administration and, on the other hand, from the *General Meet-*

ing of the principal investigators of the research network, who are the regular members of the network.

The network is supported by National Medical Associations (e. g. German Society for Psychiatry, Psychotherapy, and Nervous Diseases – DGPPN, German Society for General Medicine – DEGAM, Federal Association of Psychiatrists and Neurologists in Practices – BVDN/BVDP), and major German health insurance funds, as well as by the World Psychiatric Association (WPA). Beyond the primary funding by the BMBF, additional sponsoring (about 5 % of the budget) is provided by pharmaceutical companies for research projects (Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, Lundbeck, Sanofi-Synthelabo, Wyeth) or public relations activities of the network (additionally Astra-Zeneca, Bayer Vital, Novartis, Pfizer [as of August 2003]).

Main projects of the network

Early detection and early intervention

The Mannheim ABC study has shown that the first treatment contact of people suffering from schizophrenia is preceded by a period of manifest psychotic symptoms, on average lasting for 1 year, and a pre-psychotic prodromal period of about 5 years with increasing negative and unspecific symptoms and functional impairment (e. g. Häfner et al. 1998). Most of the social consequences of the disorder occur in this early period of the course of schizophrenia. Congruently, high-risk and population cohort studies revealed that subjects who later develop schizophrenia have mild cognitive, motor, and social deficits from early childhood on as precursors of the disorder (e. g. Walker et al. 1995; Jones et al. 1994; Parnas et al. 1993; Erlenmeyer-Kimling et al. 1995). At the same time, it has been shown that delayed treatment is associated with significant disadvantages for schizophrenia patients, often resulting in functional and social decline (e. g. Wyatt 1997; Yung et al. 1998; Bottlender et al. 2003; Bottlender and Möller 2003). Thus, in order to optimize outcome, it seems essential to recognize and treat schizophrenia patients as early as possible. Against that background, Project Network I contains six interrelated research projects targeting early recognition and intervention in subjects at risk for schizophrenia.

To establish a basis for such research, one project has developed a two-step inventory for early recognition, diagnosis and prediction of schizophrenia ("Development and evaluation of an early detection inventory", principal investigator: H. Häfner, K. Maurer, Mannheim). A short "checklist" containing 17 items was constructed as a screening instrument for identification of persons with a slightly elevated risk of psychosis in primary care institutions. If the checklist indicates predefined inclusion criteria, risk persons are referred to one of four specialized "Early Recognition Centres", which have been newly established by the GRNS in four major German cities (Cologne, Bonn, Düsseldorf, Munich). For the detailed diagnosis of these risk persons at the Early Recognition Centres, the second part of the inventory (ERI: "Early Recognition Inventory") for the assessment of prodromal symptoms is used. It contains 110 items and is primarily based on population-controlled data collected using a former inventory for the retrospective assessment of schizophrenia (IRAOS, Häfner et al. 1999, English version: 2003) and other early-detection schedules, as well as on the Bonn Scale for the Assessment of Basic Symptoms (BSABS, Gross et al. 1987). Included in the ERI is a severity by time matrix for a retrospective assessment of symptom development in monthly steps in the year prior to interview. The inventory also includes modules for assessing additional prognosis-relevant risk factors (substance abuse, delinquency, patient's functioning in everyday life situations). The necessary prospective validation of these instruments and optimization of risk assessment is currently being accomplished in two clinical early intervention studies and a conscript study within the GRNS (principal investigator: W. Maier, Bonn), as well as in two collaborating projects in Israel (principal investigators: J. Rabinowitz, R. Gan, J. Klosterkötter) and Italy (principal investigators: A. Cocchi, A. Meneghelli, H. Häfner).

For the two early intervention studies within the GRNS, two groups of risk persons are selected from the larger group of persons referred to the Early Recognition Centres, according to their presumed prodromal stage. Based on previous longitudinal observations, an "early prodromal stage" is assumed if subjects report predictive basic symptoms in the ERI (Klosterkötter et al. 2001) or if they have a first-degree relative with schizophrenia and show a marked decline in global functioning. "Late prodromal stages" are defined by the occurrence of brief limited intermittent psychotic symptoms (BLIPS) or by attenuated positive symptoms.

Persons at risk for psychosis in the early prodromal state are included into an early intervention study ("Psychological intervention for persons at risk for psychosis in the early initial prodromal state", principal investigator: A. Bechdolf, Cologne) examining the effects of a newly developed cognitive-behavioural therapy strategy for prodromal persons (Bechdolf et al. 2002; Bechdolf et al. submitted). This treatment is compared with clinical management within a randomized control design over a 24-month period regarding improvement of prodromal symptoms, prevention of social decline and prevention or delay of progression to psychosis. First results in clients having completed the 12-month intervention period indicate that cognitive-behavioural therapy showed promising effects. In this group, the observed within-group effect sizes regarding symptom reduction were up to three times higher than the effect sizes known for cognitive-behavioural therapy in patients with chronic schizophrenia and standard neuroleptic treatment ($d = 0.87$, after Rector and Beck 2001). There was evidence that cognitive-behavioural therapy may be able to prevent transition to the late prodromal state or psychosis. Albeit preliminary, these findings support the

notion that intervening in early stages of the illness is exceptionally effective (McGlashan and Johannessen 1996).

Persons in the late prodromal state of psychosis are included into a second early intervention study ("Early pharmacological and psychological intervention for late prodromal states of psychosis", principal investigator: St. Ruhrmann, Cologne), which compares the effects of atypical neuroleptic medication with amisulpride in combination with an enriched clinical management (i. e. clinical management supported by crisis intervention or family counselling in case of need, but no regular psychotherapy) to psychologically enriched clinical management alone. It is a phase-III study with an open-label, randomized parallel design with a treatment period of 2 years. Effects will be evaluated regarding improvement of prodromal symptoms, avoidance of social impairment and suppression or at least delay of progression to psychosis. Preliminary results indicate that the combination of amisulpride and clinical management already seems superior to the control treatment during the first 3 months of treatment with regard to suppression of attenuated psychotic symptoms and improvement of depression, negative symptoms and global level of functioning (Ruhrmann et al. 2002). Thus, this combination seems to be a promising approach for treatment of late prodromal syndromes.

The development of early detection instruments and the investigation of early intervention strategies is accompanied by two projects focussing on neurophysiological and neurocognitive assessments in early and late prodromal states ("Biological basis of the risk of illness", principal investigator: M. Wagner, Bonn) or functional imaging of 5-HT_{2A}-receptors in late prodromal states using positron emission tomography ("Biological basis of early pharmacological intervention", principal investigator: K. Vogeley, Bonn), respectively. The neurobiological and -psychological characterization of prodromal states of schizophrenia will add to the knowledge of the pathogenesis of the disorder; simultaneously, predictors for the progressions from the prodromes to schizophrenia can be extracted.

First-episode schizophrenia

A number of studies have shown advantages of "atypical" new generation antipsychotics compared to conventional antipsychotics in acute treatment (for review: Leucht et al. 1999), as well as in long-term treatment of schizophrenia (for review: Leucht et al. 2003a). Novel antipsychotics were often found to be more effective with regard to treatment of negative symptoms, and showed a more favourable profile of extrapyramidal side-effects and beneficial effects on cognitive dysfunctions, depression and compliance (Möller 2000; 2003). However, interpretation of results obtained by many studies comparing new generation antipsychotics with conventional antipsychotics is restricted, as the conventional neuroleptics mostly have been administered in rather high dosages. Meta-analyses suggest that atypical and conventional antipsychotics are equivalent on symptom reduction and tolerability if the latter are administered in low dosages (Geddes et al. 2000, but see Davis et al. 2003). Low-potency neuroleptics even might not induce more extrapyramidal side-effects under such a low-dose strategy than new generation drugs (Leucht et al. 2003b). Though recommendations have already been published that "atypical antipsychotics should be considered alongside the existing traditional (typical) medicines as one of the first choice options to treat people with newly diagnosed schizophrenia" (NICE 2002), long-term studies especially with first-episode patients are still lacking (Geddes 2002). Beyond this uncertainty regarding the best kind of neuroleptic treatment, for the special group of first-episode patients it is, furthermore, unclear how long treatment should be continued after cessation of the first acute phase (Sheitman et al. 1997; Wyatt et al. 1998). Published guidelines recommend treatment durations of a minimum of 1 year (e. g. APA 1997; DGPPN 1998), the appropriate duration of further treatment in case of symptom remission, however, has not been adequately provided.

Against that background, a comprehensive acute and long-term treatment study in patients with first-episode schizophrenia has been initiated within Project Network II of the GRNS. This network study also contains six interrelated subprojects conducted in up to 13 German university hospitals. The backbone of the study is a prospective double-blind, randomized, parallel-group comparison of risperidone as a new generation antipsychotic with haloperidol as a conventional antipsychotic. Both drugs are administered in rather low daily dosages of 2 to a maximum of 8 mg/day during the 8 weeks of the acute treatment study ("Optimization of acute treatment in first-episode schizophrenic patients", principal investigator: H.-J. Möller, Munich). Besides retainability of patients under such low-dose strategies with regard to the necessary reduction of positive symptoms, this study is mainly interested in differential drug effects on negative and affective symptoms, cognitive impairments, as well as in undesirable side-effects.

After stabilization, patients are transferred to a subsequent 2-year long-term treatment study ("Pharmacological long-term treatment strategies for relapse prevention in first-episode schizophrenia", principal investigator: W. Gaebel, Düsseldorf), where daily dosages are reduced to 2–4 mg/day, as possible. To investigate the necessary duration of long-term treatment in first-episode patients, patients completing the first treatment year without relapse are randomly allocated to either maintenance treatment or stepwise drug discontinuation in the second treatment year. In the case of impending reexacerbations, early intervention strategies are additionally used in the second treatment year to prevent relapses. To this end, patients are assessed fortnightly throughout the 2-year study period, in order to closely monitor clinical course and possible prodromal symptoms. Within the framework of the vulnerabil-

ity-stress-coping-(VSC) model, prodromal symptoms are taken as early indicators of an impending reexacerbation and can, thus, be used as predictors of relapse to guide early intervention. Despite a number of negative results in multi-episode patients (Gaebel 1996), a reanalysis of a previous study on long-term treatment strategies (ANI-study) suggests that prodrome-guided early intervention strategies may after all be advantageous especially for first-episode patients (Gaebel et al. 2002b). Accordingly, an improved instrument for the assessment of prodromal symptoms as well as an empirically based algorithm to trigger the onset of early intervention was developed in a further subproject of the first-episode study in close cooperation with PN I. In addition to prodromal symptoms, this early intervention algorithm takes into account mild positive symptoms, global clinical deterioration, global functioning, the occurrence of stressful life-events, as well as the clinician's global assessment of the patient's risk for relapse. If the algorithm indicates an impending reexacerbation, patients are treated either by means of resumption or augmentation of neuroleptic treatment (depending on the basic treatment strategy of discontinuation or maintenance treatment) or by means of treatment/additional treatment with the benzodiazepine lorazepam. This random, double-blind comparison should contribute to the open question whether prodromes are unspecific consequences of stress experience treatable with benzodiazepines or have to be regarded as more specific, prepsychotic symptoms requiring neuroleptic treatment (e. g. Carpenter et al. 1999).

In five of the 13 centres, the pharmacological treatment in the first year of long-term treatment is supplemented by one of two psychological treatment strategies (Project "Psychological intervention for relapse prevention in first-episode schizophrenia", principal investigator: St. Klingberg, Tübingen). Patients are randomly assigned to either a comprehensive cognitive behavioural treatment containing several modules aiming at cognitive rehabilitation, stress reduction and strengthening of coping abilities especially assembled and designed for first-episode schizophrenia or to information centreed psychoeducation. Besides relapse rates after 1 and 2 years, negative symptoms, social adaptation and quality of life as well as neuropsychological functioning are assessed as main outcome measures.

Neurocognitive and neuromotor vulnerability markers, biochemical indicators of stress reactivity and brain morphological parameters are assessed in a separate subproject at the beginning and after 1 and 2 years of long-term treatment ("Biological mechanisms of relapse", principal investigator: W. Gaebel, Düsseldorf). Additionally, neurofunctional correlates of emotional and cognitive impairments are assessed in eight participating centres by means of functional Magnetic Resonance Imaging (fMRI, "Functional brain indicators of relapse", principal investigator: F. Schneider, Düsseldorf).

By the end of August 2003, 255 patients had been included into the acute treatment phase and 152 had entered the long-term study; 48 patients had already reached the second year of treatment. Since the targeted sample size contains a total of 180 patients entering the long-term study with at least 70 patients to be included into the second year of treatment, enrolment of patients will be continued until the beginning of 2004. Preliminary findings so far suggest that the treatment with low dosages of antipsychotics is feasible and effective and leads to a significant improvement of positive, negative and prodromal symptoms in first-episode schizophrenic patients. Because medication will be unblinded only at the end of the whole study, comparison of differential treatment or side-effects between both drugs is not yet possible. However, until now, none of the patients has fulfilled the criteria for relapse within the first year of treatment.

The acute and long-term treatment studies are supplemented by the so-called "Basic study" ("Acute course and 2-year follow-up in schizophrenic illness under present treatment and care conditions", principal investigator: H.-J. Möller, Munich), which is a prospective multicentre study on the acute and mid-term course and outcome of patients with first and multiple episodes of schizophrenia under naturalistic treatment conditions. In this respect, the "Basic study" serves as a kind of "ecological validation" of the intervention studies on first-episode patients. Moreover, the "Basic study" serves as a second-line monitoring opportunity in order to follow-up those first-episode patients who could not be enrolled in the acute treatment study or the subsequent long-term treatment study or dropped out from these studies. A major aim of the "Basic study" is a multidimensional description of the acute and 2-year course and outcome in patients with first and multiple episodes of schizophrenia under naturalistic treatment conditions. One focus of the study can be seen in the investigation of the development of unfavourable courses of the schizophrenic illness, particularly the development of therapy-resistant positive symptoms and the occurrence of persisting negative symptoms, depression, suicidal tendencies, side-effects and other adverse events. Considering that treatment resistance or non-response affects a substantial number of patients, there is not only a need for improved strategies for an earlier identification of these patients, but also a need for the establishment of alternative treatment strategies. In this respect, a further aim of the "Basic study" is to identify potential predictors for therapy-non-response and the integration of these predictors into a multidimensional prognostic model, including clinical, anamnestic, biological and psychosocial data.

Quality assurance in inpatient and outpatient care

Quality assurance and quality improvement guarantee optimal care in accordance with the state-of-the-art knowledge under consideration of available resources. Optimizing treatment of schizophrenia through imple-

mentation of guidelines and quality assurance is essential for early and acute as well as long-term and chronic phases of schizophrenia. This becomes evident when considering findings that only 40–50 % of schizophrenia patients are treated according to scientific standards and treatment guidelines (Gmür and Tschopp 1988; Lehmann and Steinwachs 1998). Often relapse prevention with neuroleptics is inadequate and insufficient because neurological and psychiatric practitioners overestimate the potential side-effects of long-term medication (Osterheider et al. 1998). Although several treatment guidelines for schizophrenia have been published over the last years (e. g. Germany: DGPPN 1998; USA: APA 1997), it is expected that only a case-focussed implementation of these guidelines will lead to an improvement in outcome quality measures (Grimshaw and Russell 1993).

Therefore, two projects targeting quality assurance either in inpatient care or in outpatient care have been initiated within the GRNS as part of PN II. The first of these projects ("Guideline-supported quality management in inpatient acute treatment of schizophrenia patients", principal investigator: W. Gaebel, Düsseldorf) targets the systematical development, implementation and evaluation of specific measures of quality management in inpatient treatment of schizophrenia at eight psychiatric hospitals, mostly district hospitals. Using an experimental control group design with pre- and post assessments, quality-orientated interventions according to the concept of Total Quality Management (TQM) and with reference to the German treatment guidelines (DGPPN 1998) are compared in four experimental hospitals with a mere successive documentation of structural parameters (hospital and patient characteristics), treatment and outcome in four control hospitals. Experimental hospitals receive feed-back by means of a comparative benchmarking based on the documentation data obtained in the four experimental hospitals, and are guided to implement quality circles for specific problem areas identified from the benchmarking process.

Up to now, the data of 600 patients have been analysed showing several positive effects of the internal and external quality management procedures. For example, after quality circle intervention, fewer side-effects were found at the time of discharge in the experimental group compared to the control group. This could be due to a decrease in prescription of typical neuroleptics, which could also be found in the experimental group.

The second project ("Guideline-supported quality management in psychiatric practices", principal investigator: W. Gaebel, Düsseldorf) follows a similar approach for optimizing outpatient treatment of schizophrenia. The main focus is on implementation of guidelines, but also other elements of internal (documentation system, monitoring) and external quality management (benchmarking) are being established in hospital-associated networks of private psychiatric practices in three different German cities (Düsseldorf, Freiburg, Munich). A graduated intervention system was implemented and evaluated in four groups of practices. The experimental group uses a computer-based documentation system with implemented treatment guidelines and decision-support, and receives comparative benchmarking as described for the inpatient project. The computerized documentation system QMax (Menke et al. 2001) draws the attention of the physician to the treatment guidelines by means of a pop-up window showing the relevant guideline algorithm whenever the entered data indicate critical changes in the patient's clinical status. Two further experimental groups use either the computer-based documentation system without implemented guidelines and benchmarking, or paper and pencil documentation with additional organization in quality circles. A control group uses paper and pencil documentation without additional organization in quality circles.

So far, 583 patients with schizophrenia treated by 55 psychiatrists for at least 16 months have been assessed. At the end of the observation period, the patients of the experimental group showed a significant reduction in the PANSS-subscores of general, positive and negative symptoms. Similar results have been obtained in the group of practices working with quality circles. However, in those practices merely documenting their treatment either computer-based or with paper-pencil, no such changes were found.

Besides their scientific merit, these quality assurance projects comprise intensive interaction between the participating institutions which goes far beyond the transfer of knowledge, especially knowledge on the most current treatment guidelines, which, additionally, can be introduced, tested and revised in these projects. Thus, the projects bring forward the "vertical networking" between research and care institutions, as well as collaboration between participating practices or hospitals, respectively (horizontal networking).

Molecular- and pharmacogenetic research

Genetic variation explains more than 50 % of the etiological variance of schizophrenia. Genetic variants are also likely to explain a substantial proportion of the interindividual variations in response to neuroleptic drugs (therapeutic as well as side-effects). There is strong evidence that multiple genes are involved in the manifestation of schizophrenia as well as in the response to neuroleptic drugs (Maier 2003). Up to now, the specific genes involved in etiology and treatment response have been unknown; however, a few hot positional candidates for the etiology of schizophrenia have recently emerged (dysbindin, neuregulin, G72).

Nowadays, the bottleneck for the detection of disposition, modulating and predictive genetic variants is the availability of informative samples; these have to be large, given that the expected gene effects are probably small and given that alleles may frequently play a crucial role. A decisive additional condition to understand the impact of disposition genes on the pathophysiology of

the disorder is a comprehensive neurobiological characterization of the phenotype.

The GNRS displays a unique opportunity to recruit appropriately sized clinically and neurobiologically well-characterized samples for the search of these genetic variants.

In addition, large patient samples will undergo refined characterization with respect to response to medication and course of the disease within controlled treatment trials. The project "Molecular genetics and pharmacogenetics" (principal investigator: W. Maier, Bonn) aims to establish a core facility for cell- and DNA banks by obtaining blood samples from patients participating in the prospective treatment studies of the GRNS. It targets the identification of genetic markers contributing to manifestation and course of schizophrenia, as well as predictors for response and occurrence of side-effects. The received DNA and cell-line samples are used for association studies for known and so-far unknown gene markers putatively involved in the pathogenesis of schizophrenia and in the development of desired antipsychotic and undesired drug side-effects (dopamine receptor genes DRD2,3,4; serotonin receptor genes 5HT1A, 2A, 2C, 7; serotonin transporter gene 5HTTLPR, tryptophane hydroxylase, COMT; MAO; tyrosine hydroxylase, NOTCH4 and others). The established DNA- and cell bank will provide an enduring facility for studying the genotype-phenotype relationship for any forthcoming disposition or modifier gene. Thus, the DNA bank in general will create possibilities to gain more insight into underlying determinants of the illness and to contribute to an individualized genotype-tailored therapy in the long term.

In order to generate new pharmacogenetic candidate genes, we search for differential expression of genes induced by neuroleptics in model cell systems (cultured cell-lines of human medulloblastoma cells, human neuroblastoma cells and human lymphoblast cells). For example, to investigate genes affected in their expression when treated with haloperidol and risperidone, differentiated human dopaminergic neuro-blastoma cells were tested in vitro by using cDNA microarrays, quantitative RT-PCR and SELDI-ProteinChip-technology at different non-toxic doses and at different points in time. Genes which are involved in complex signal transduction pathways and in the dopaminergic pathway (e. g. dopamine beta-hydroxylase, MAO, COMT, DRD2) and so far not conceived as candidate genes could be identified (v. Widdern et al. in preparation).

Perspectives

The *German Research Network on Schizophrenia* has now been funded for about 3 years. After successful mid-term evaluation by the Scientific Advisory Board, further funding has recently been granted by the BMBF until mid 2005. Thereafter, the network will finance itself by other resources. Since most of the studies conducted within the GRNS are long-term studies lasting up to 5 years, scientific results are to be expected primarily at the end of the funding period. However, significant structural improvements regarding intensified collaboration between and within the research and care levels have already been achieved. Moreover, all projects have successfully been implemented, so that significant surplus effects and promising results can be expected during the next years.

The network is open-minded to complement with other national and international networks. In this regard, first steps have been taken by organizing joint symposia at major international conferences (World Congress of Biological Psychiatry, 2001, Berlin; Congress of the Association of European Psychiatrists, 2002, Copenhagen) together with other networks, like "Human Brain Informatics" (HUBIN, Speaker: G. Sedvall, Sweden), "European First Episode Study" (EUFEST, Speaker: R. Kahn, Netherlands), "European Prediction of Psychosis Studies" (EPOS, Speaker: J. Klosterkötter, Germany) and the "Clinical Antipsychotic Trials of Intervention Effectiveness" (CATIE, Speaker: J. Lieberman, USA).

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