

# Schizophrenia and negative symptoms – burden of disease in seven Central and Eastern European (CEE) countries. Literature review and retrospective data collection – project design and rationale



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## ABSTRACT

**Objective:** Schizophrenia is a serious public health problem: it affects approximately 1% of world's population and is a leading cause of disability. The main objective was to develop a report concerning burden of schizophrenia with special attention to negative symptoms in seven Central and Eastern European countries.

**Methods:** The project consisted of two phases: literature review and retrospective data collection. The literature review involved a search for published literature in international databases and country-specific data from local sources in relation to: epidemiology, clinical guidelines, standards of care, cost of illness, resource utilisation, health related quality of life and caregiver burden. The second phase involved retrospective data collection on the basis of patients' medical cards and gathering the medical experts' opinions. In each country 3–6 medical centers participated in the project. Psychiatrists completed questionnaires with data from randomly selected medical cards. Statistical analysis was used to test differences between included centers and countries with regards to the treatment of schizophrenia.

**Results:** The results of literature review served as the framework for retrospective data collec-

tion. For the second phase of the project, the sample size included about 1,000 patients' cards from participating countries showing the daily clinical practice of schizophrenia treatment. Results from the project were presented and discussed with medical experts and key opinion leaders during local workshops.

**Conclusion:** The project addresses relevant issues related to the burden of schizophrenia and complements data presented in the literature with additional data gathered in clinical practice, especially in the area of schizophrenia negative symptoms.

## BACKGROUND

Schizophrenia is one of the most common psychiatric disorders, estimated to affect from 0.4% to 1.4% [1,2] of the population and has a mean annual incidence of 11-16 per 100,000 [1-3]. Schizophrenia affects men and women equally; however, there is an earlier onset in males [4]. Due to its early onset and chronic course, schizophrenia is a relatively frequent and burdensome disease. Moreover, schizophrenia affects both patients and, indirectly, their caregivers [5-7]. Schizophrenia is broadly characterized by three domains of psychopathology, including negative symptoms (eg. social withdrawal, lack of motivation and emotional reactivity), positive symp-



toms (hallucinations, delusions) and cognitive deficits (working memory, attention, executive function) [8]. Some data indicate that negative symptoms are the important cause of poor patient functional outcomes and impairments in quality of life [9,10]. Available antipsychotics have limited impact on negative symptoms and their treatment is considered a key unmet medical need in the schizophrenia [11]. The main objective of the project was to prepare a comprehensive report on the burden of schizophrenia, with particular focus on negative symptoms of the disease in seven chosen Central and Eastern European countries (CEE): Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia. Other objectives were to verify the gathered data during local workshops and to discuss the results with the medical experts and key opinion leaders in each country involved to understand better the current practice and needs in the schizophrenia area.

## METHODOLOGY

### *Study design*

The project Schizophrenia and Negative Symptoms – Burden of the Disease in Seven Cen-

tral and Eastern European (CEE) Countries was designed as a retrospective, multicenter and non-interventional project. It was divided into two parts:

1. Literature review, which considered data from international databases and from local data sources
2. Retrospective data collection performed in each country of interest based on unified questionnaires

The results of the retrospective data collection, with data from the literature review as a background, were presented and discussed during the workshops – first, at seven country-specific workshops, then, additionally, one final cross-country workshop is planned as a final summary of the project. Results were also shared at international conferences and are planned to be published in regional and international journals.

### *Literature review: international and local*

The aim of the literature review was to gather relevant and current information regarding burden of schizophrenia and, in particular, negative symptoms of schizophrenia. As a first step the following international data sources were searched using an English-language search strategy:

- [PubMed \(MEDLINE via PubMed\)](#)
- [Cochrane Library \(all libraries\)](#)
- [Centre for Review and Dissemination \(CRD\): Database of Abstracts of Reviews of Effects \(DARE\), NHS Economic Evaluation Database \(NHS EED\), Health Technology Assessment \(HTA\) Database](#)
- [National Guidelines Clearinghouse](#)
- [National Institute for Health and Clinical Excellence \(NICE\)](#)
- [European Medicines Agency \(EMA\)](#)

Publications found as a result of the search underwent a two-step selection process. First, based on the titles and abstracts of all studies retrieved from the search, the relevant records were selected. In the second step, full text versions of the papers included in the initial screen-

ing phase were examined for inclusion within the review. To focus on the most current publications the literature search was limited to papers published after 1995, but no language restrictions were applied. The detailed inclusion and exclusion criteria are presented in Table 1.

The second part of the literature review comprised a search of local databases in order to identify relevant data published in local languages. The following local data sources were searched (if available):

- Websites of HTA agencies,
- Patient registries,
- National medical journals,
- Databases of National Health Service,
- National/Central Statistical Office,
- National Psychiatric Association,
- Local psychiatric websites,
- Other relevant data sources.

The information gathered in each country by a local expert were translated to English, then recorded in a predefined data extraction sheet and finally incorporated in the report. A search was performed to include publications dedicated to the following areas:

**Definitions of schizophrenia** – classifications of the disease; definitions of positive, negative and cognitive symptoms; definitions of different types of schizophrenia,

**Epidemiology** – incidence and prevalence; mortality; risk factors; age at disease onset; demographic characteristics of schizophrenia patients – gender distribution, marital and social status,

**Disease management of schizophrenia focusing on the negative symptoms** – clinical guidelines; recommendations; standard of care/treatment patterns: pharmacotherapy, psychotherapy; compliance/adherence to treatment,

**Economic and humanistic burden of the disease** – cost data based on information about: drugs used in schizophrenia treatment, hospitalizations, outpatient ambulatory procedures,

Table 1. Inclusion/exclusion criteria for literature review

|                      | INCLUSION CRITERIA   | EXCLUSION CRITERIA   |
|----------------------|--|--|
| PUBLICATION TYPE     | Guidelines and recommendations on schizophrenia treatment, review and systematic review  | Other than: review, systematic review review and systematic review   |
|                      | For epidemiological data: relevant review and systematic review  |  |
|                      | Quality of life – primary studies  | Other than primary studies   |
|                      | Cost and burden of disease, stigmatization and discrimination – primary and secondary studies, review and systematic review  | Other than: review, systematic review, guidelines, practical guidelines, burden of disease, meta-analysis, economic analysis, cost studies |
| YEAR OF PUBLICATION  | 1995 - present   | Studies published before 1995  |
| COUNTRIES CONSIDERED | Poland, Slovenia, Estonia, Slovakia, Hungary, Serbia, Croatia.<br><br>In case of lack of relevant publications for these countries and in order to complete background, the data from other European countries were included |  |
| CONDITION            | Schizophrenia (F.20 according to ICD-10 classification)  | Schizotypal and delusional disorders (F.21-F.29 according to ICD-10 classification)  |

outpatient ambulatory visits, GP visits, diagnostic and monitoring tests and procedures, costs of lost productivity, rehabilitation, social worker visits, etc.; resource utilization data (drug doses, length of inpatient stays, number of hospitalizations per patient per year, number of outpatient visits per year, number of monitoring tests per year, patterns of AE treatment, choice of antipsychotic drugs in the first and second line of treatment and in refractory patients, compliance and adherence data, etc.); HRQoL (health related quality of life) data; caregiver’s burden.

**List of reimbursed drugs with official price tariff and the level of reimbursement (to estimate average price from NHF and patient perspectives) for: neuroleptics, antidepressants, mood stabilizers and anxiolytics (from databases of NHS).**

Based on the relevant papers and data identified as a result of the literature search, the report on burden of schizophrenia was prepared. The country-specific data from the chosen CEE countries were in scope of this report and, in case of lack of relevant records for the CEE region, worldwide data were also included.

## STUDY AREA AND PARTICIPANTS

Seven CEE countries were chosen to participate in the project: Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia (Figure 1).



Figure 1. Distribution of countries involved in the project

In each country 3 – 6 medical centers were involved in the project: psychiatric hospitals with ambulatory and general hospitals with mental wards. The choice of sites reflected the management of schizophrenia in particular countries, and the number of reviewed medical records allowed for a representative size of patient populations in each of the countries for further discussion of the findings.

## RETROSPECTIVE DATA COLLECTION

Retrospective data collection was performed by filling in two types of questionnaires:

1. Based on data from patients’ medical records
2. Insight by local medical experts specializing in psychiatric practice from each country of interest.

The collected data reflected the daily practice of medical diagnostic and therapeutic procedures used in patients with schizophrenia, with emphasis on negative symptoms in the local conditions.

Between 5 and 9 experts from each country were involved in the retrospective data collection. Involved psychiatrists had at least 8 – 10 years of experience in the treatment of schizophrenia and treated at least 10 patients with schizophrenia per month. An additional assumption was that doctors had practices in both hospitals and outpatient clinics, or at least they had access to the patients’ outpatient and inpatient records.

Each expert involved in the project completed between 10 and 30 questionnaires based on patient cards. Where possible, the reviewed data covered the whole disease history; in other cases the last 5 years of patient treatment data were gathered. Patient data were anonymously collected in the questionnaires.

The choice of patient cards was performed randomly by each of the experts according to the same principles:

1. Patients treated for schizophrenia during the last 5 years
2. Where possible, the proportion of patient medical cards coming from hospitals and outpatient clinics reflected the proportion of patients treated in hospital (inpatients) and outpatient settings in each particular country
3. It was assumed that the number of newly diagnosed patient cards (from each specialist) should not exceed 20% of selected medical cards

The exemplary questions are presented in Table 2.

Table 2. Sample questions from questionnaires

| PATIENT MEDICAL CARD  | EXPERT INSIGHT   |
|---|--|
| 1.1. Age<br>1.2. Sex<br>1.3. BMI  | 1.1. Country<br>1.2. Center/clinic<br>1.3. Experience in schizophrenia treatment [years]<br>1.5. How many patients with schizophrenia have been treated in your unit during the last year?   |
| 2.2. Year/age* of first diagnosis of schizophrenia<br>2.3. Year/age* of starting treatment of schizophrenia<br>2.7 Type of schizophrenia (according to ICD-10 classification)<br>2.8 Presence of any primary negative symptoms during the course of schizophrenia<br>2.9. Type of primary negative symptoms<br>2.14. Year/age* of onset of primary negative symptoms<br>2.16. Presence of any positive symptoms during the course on illness<br>2.19 Number of psychotic relapses | 2.1. What is the percentage of individuals with diagnosed schizophrenia among all patients with schizophrenia in your country (using ICD-10)?<br>2.2. What is the proportion of non-compliant patients with diagnosed schizophrenia?<br>2.3. What is the proportion of patients with different types of schizophrenia using ICD-10 in your ward/clinic (patients treated by you) [%]?<br>2.4 What is the percentage of treated patients with schizophrenia who suffer from any primary negative symptoms?<br>2.11. What is the percentage of treated patients with diagnosed schizophrenia who have/had suicidal thoughts or attempts?<br>2.11.1. What is the percentage of treated patients (with schizophrenia) who are experiencing primary negative symptoms and who have/had suicidal thoughts or attempts?<br>2.12. What is the percentage of treated patients with diagnosed schizophrenia who had a relapse of the disease during the last 5 years?<br>2.12.1. What is the percentage of patients suffering from primary negative symptoms who had a relapse of the disease during the last 5 years? |
| 4.1. Civil status<br>4.2. Employment status<br>4.3. Education<br>4.4. Residence situation<br>4.5. Patient incapacitated<br>4.6. Patient had to stop working/learning because of disease   | 4.1. How many employed patients have to stop their work/education because of the disease [%]? In pts with schizophrenia/schizophrenia patient with primary negative symptoms<br>5.1.1. What is the standard treatment pattern as the first course? (please describe)\<br>5.1.2. What is the proportion of pts who receive only psychological/psychosocial support (without pharmacotherapy) as the first course of treatment?<br>5.1.4. Which of antipsychotic medications are used as the first course of treatment and in what doses?<br>5.1.5. What are the most common reasons for treatment discontinuation?<br>5.4.1. What is the type of hospital where patients stay during hospitalization?<br>5.9.3. Occurrence of AEs and typical treatment of AEs  |

Length of schizophrenia and severity of disease were not defined in order to obtain a representative sample of patients.

The questionnaire based on patients’ medical records gathered data regarding patient profile, type of schizophrenia, duration and severity of illness, characteristics of the disease – type of presenting symptoms during the course of disease, co-morbidities and relapses. The questionnaire also included data on applied treatment, including hospitalizations, pharmacotherapy, psychotherapy and other forms of treatment. Separate parts focused on the treatment of negative symptoms and the social status of patients with schizophrenia.

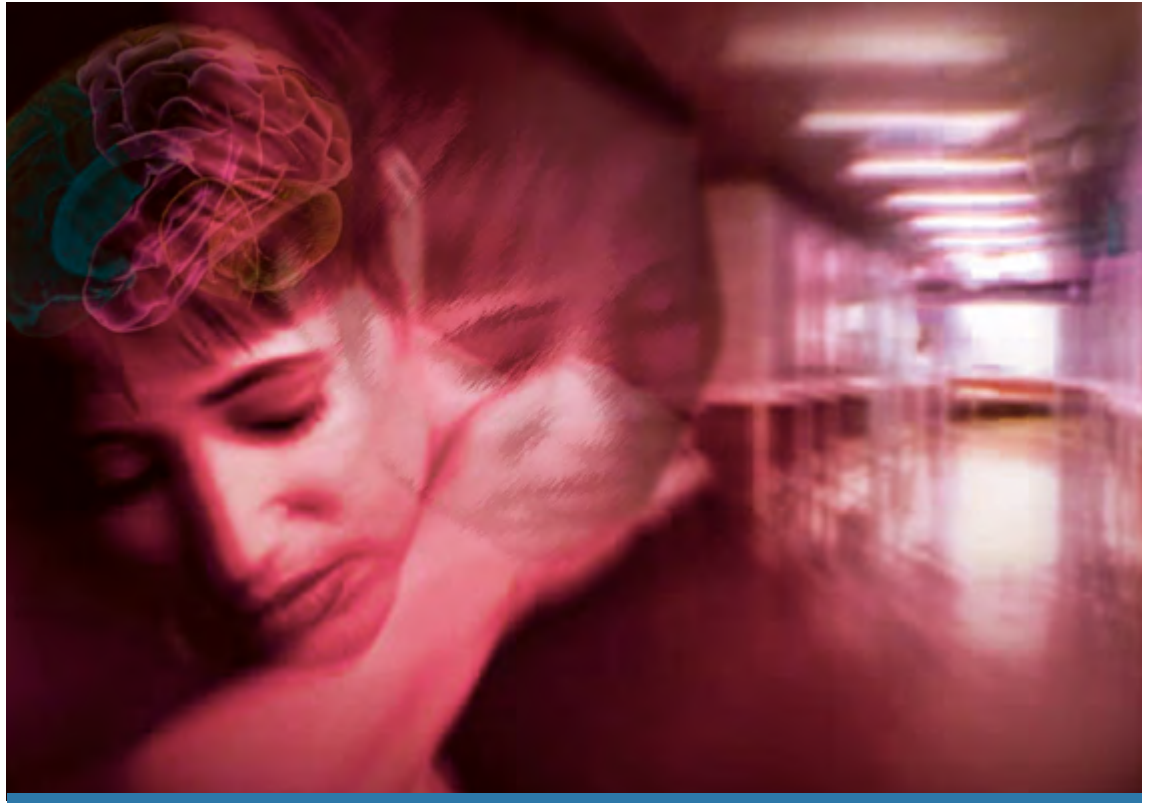
The second type of questionnaire used in the project was one specially designed to collect the experts’ opinions. In some centers a few experts from one site were allowed to complete together a single questionnaire regarding the specialist in psychiatry practice insight.

This questionnaire was completed to reflect experts’ opinions based on their personal experience with patients with schizophrenia and knowledge from medical practice. The questionnaire focused on data regarding psychiatrists’ experience in the treatment of schizophrenia, characteristics of the schizophrenia population in each country of interest, social aspects of the disease in the general population of schizophrenia patients and in the population of patients who suffer from negative symptoms of schizophrenia. Data were also collected concerning treatment patterns, resource use and adverse event management.

After collecting all questionnaires, the accuracy of the data was verified, and all findings were discussed and agreed between the experts. All explanations of the information provided were recorded to be included into the final report.

In the final step all data from the questionnaires were processed, analyzed, discussed and summarized in a final report.

least one variable and the Fisher exact test indicated dependency between the variables, then a post hoc analysis was applied (post hoc Fisher exact test with Bonferroni correction). The dependency between the data was visualized with Forest plots of proportion. Continuous data were analyzed using ANOVA or the Mann–Whitney–Wilcoxon test. The choice of test depended on the assumptions that were met by the data. Boxplots were used to display differences between the subgroups.



THE AIM OF THE ANALYSIS WAS TO DETECT ALL SUBSTANTIAL DIFFERENCES BETWEEN THE RESULTS OF QUESTIONNAIRES GATHERED FROM DIFFERENT CENTERS/COUNTRIES AND TO DETECT ASSOCIATIONS BETWEEN PARTICULAR QUESTIONS.

## STATISTICAL ANALYSIS

The aim of the analysis was to detect all substantial differences between the results of questionnaires gathered from different centers/countries and to detect associations between particular questions. This was conducted independently for each question in the questionnaire. The methodology was chosen based on the type of data elicited by a particular question (categorical and/or continuous data). A contingency table was used to summarize categorical data. An analysis of contingency was performed with the Fisher exact test to verify if there were non-random associations between the two categorical variables. If there were more than two categories for at

## WORKSHOPS

The workshops were divided into two parts. The first part of the workshops consisted of separate meetings in each country of interest to present local results of the retrospective data collection. The second part of the workshops will convene representatives of all countries participating in the project. The main objective for the workshops scheduled in each country was to present and discuss with all the involved experts the collected data from all parts of the project – literature review, expert opinions and retrospective data collection. Other aims of the workshop meetings were to clarify ambiguous wording, to validate the collected data and to present the collective

application. The objective of the final cross-country workshop is to compare collected data between involved countries: mainly to identify the trends and similarities, but also to indicate the differences and outliers.

**RESULTS: SUMMARIES FOR EACH COUNTRY AND CROSS-COUNTRIES**

Retrospective data collection was based in total on more than 1,000 patient medical cards and about 30 questionnaires completed on the basis of experts' opinions. The numbers of questionnaires and experts involved in the project are presented in Table 3.

*The deliverables of the project were:*

- Literature review report,
- Report summarizing the results for each country of interest separately and cross-countries findings,
- Presentations for the workshops.

As a final step of the project posters regarding the findings were presented at international meetings and conferences, and publications regarding cross-country comparisons of data obtained, as well as country-specific results, are planned to be publicly available.

*Table 3. Summary of involved sites, experts and questionnaires (final number of questionnaires can differ slightly as the project is still ongoing)*

| COUNTRY      | NUMBER OF INVOLVED CENTERS | NUMBER OF INVOLVED EXPERTS | NUMBER OF QUESTIONNAIRES FROM PATIENT CARDS | NUMBER OF QUESTIONNAIRES FROM EXPERTS' OPINIONS |
|--------------|----------------------------|----------------------------|---|---|
| CROATIA      | 5                          | 5                          | 150   | 5   |
| ESTONIA      | 3                          | 9                          | 150   | 3   |
| HUNGARY      | 4                          | 7                          | 150   | 7   |
| POLAND       | 6                          | 7                          | 165   | 6   |
| SERBIA       | 6                          | 7                          | 150   | 7   |
| SLOVAKIA     | 4                          | 5                          | 81  | 4   |
| SLOVENIA     | 3                          | 9                          | 190   | 1   |
| <b>TOTAL</b> | <b>31</b>                  | <b>49</b>                  | <b>1036</b>                                 | <b>33</b>                                       |

## CONCLUSION

The project with the employed methodology will allow a comprehensive platform from which an assessment of the burden of schizophrenia to patients/caregivers/healthcare systems can be further analyzed. ■

## TIMETABLE, PARTICIPATING UNITS AND FUNDING

*The project was initiated and funded by Roche.*

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