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Epidemiology and Treatment Guidelines of Negative Symptoms in Schizophrenia in Central and Eastern Europe: A Literature Review

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Abstract: *Aim*: To gather and review data describing the epidemiology of schizophrenia and clinical guidelines for schizophrenia therapy in seven Central and Eastern European countries, with a focus on negative symptoms. *Methods*: A literature search was conducted which included publications from 1995 to 2012 that were indexed in key databases. *Results*: Reports of mean annual incidence of schizophrenia varied greatly, from 0.04 to 0.58 per 1,000 population. Lifetime prevalence varied from 0.4% to 1.4%. One study reported that at least one negative symptom was present in 57.6% of patients with schizophrenia and in 50–90% of individuals experiencing their first episode of schizophrenia. Primary negative symptoms were observed in 10–30% of patients. Mortality in patients with schizophrenia was greater than in the general population, with a standardized mortality ratio of 2.58–4.30. Reasons for higher risk of mortality in the schizophrenia population included increased suicide risk, effect of schizophrenia on lifestyle and environment, and presence of comorbidities. Clinical guidelines overall supported the use of second-generation antipsychotics in managing negative symptoms of schizophrenia, although improved therapeutic approaches are needed. *Conclusion*: Schizophrenia is one of the most common mental illnesses and poses a considerable burden on patients and healthcare resources alike. Negative symptoms are present in many patients and there is an unmet need to improve treatment offerings for negative symptoms beyond the use of second-generation antipsychotics and overall patient outcomes.

Keywords: Epidemiology, guidelines, mortality, negative symptoms, pharmacotherapy, schizophrenia.

INTRODUCTION

Schizophrenia is a serious public health problem and is ranked among the most disabling diseases in the world [1]. It is broadly characterized by three domains of psychopathology: positive symptoms (hallucinations, delusions), negative symptoms (social withdrawal, lack of motivation and emotional reactivity) and cognitive deficits (working memory, attention executive function) [2]. The worldwide prevalence of schizophrenia is estimated at approximately 1% [3]. Schizophrenia is one of the most costly mental disorders in terms of human suffering and societal expenditure [4].

At any point of time, negative symptoms affect up to 60% of patients with schizophrenia [5], with 30% having primary negative symptoms that are sufficiently prominent to warrant clinical attention [6, 7]. Currently available antipsychotics are not indicated for the treatment of negative symptoms; therefore, many patients experience persistent negative symptoms after their positive symptoms have been controlled [8]. Negative symptoms impact patients' ability to live independently, to perform activities of daily living, to be socially active and maintain personal relationships, and to work or study [9]. In addition, the severity of negative symptoms is often a predictor of poor patient functioning [9, 10].

While a number of studies have characterized the epidemiology of schizophrenia at a country-level, differences among countries, particularly regarding perceptions of the negative symptoms of schizophrenia, have not been explored in depth. Furthermore, understanding of local and international treatment guidelines for the management of negative symptoms is lacking.

OBJECTIVES

A comprehensive literature review was undertaken to gather data on the epidemiology of schizophrenia and in particular, the negative symptoms of schizophrenia in seven

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Central and Eastern European (CEE) countries: Croatia, Estonia, Hungary, Poland, Serbia, Slovakia and Slovenia.

This project is the first of its kind to characterize the epidemiology and treatment of schizophrenia in these CEE countries. An analysis in Western Europe has been described in several previous studies, including the European Schizophrenia Cohort (EuroSC) study, with data from France, Germany and the UK (N=1208 patients) and the European multinational EPSILON study which was conducted in The Netherlands, Denmark, the UK, Spain and Italy (N=404 patients) [11-14]. These countries were selected because collectively they may offer a new perspective from which to consider schizophrenia treatment and epidemiology.

Search criteria included literature relating to epidemiology, clinical guidelines and recommendations, current standards of care, costs of illness, resource utilization, health-related quality of life, and stigmatization and discrimination related to schizophrenia. This manuscript will focus on epidemiological considerations and current clinical guidelines and recommendations for the treatment of negative symptoms. Additional results from this research, such as the quality of life findings, will be published separately.

METHODS

The literature review included publications from 1995 to 2012 that are indexed in MEDLINE (via PubMed), the Cochrane Library (all libraries) and the UK Centre for Reviews and Dissemination. The search strategy was developed using the term 'schizophrenia' and its synonyms were targeted through specific filters to identify the following:

- Publications from key countries: the country name was combined with the result of the schizophrenia synonyms search.

- Relevant papers on the negative symptoms of schizophrenia: a filter 'negative symptoms' and its synonyms was added.

- Publications concerning schizophrenia epidemiology: a filter was applied using the terms 'epidemiology', 'prevalence' and 'incidence'.

- Publications concerning clinical practice, treatment options, and standard care: a filter on 'antipsychotic drugs' combined with 'psychosocial therapy' and 'psychotherapy' and its synonyms according to MeSH terms was applied.

Relevant websites, such as the National Guidelines Clearinghouse, National Institute for Health and Care Excellence and European Medicines Agency, were also searched using the terms: 'schizophrenia' and 'negative symptoms' in order to identify guidelines and recommendations for drugs and treatments used in European countries for schizophrenia, and other relevant papers.

Additionally, in each of the seven countries of interest, searches were performed to identify relevant local-language publications. Data sources included health technology assessment agencies, patient registries, national medical journals, national health services, national/central statistical offices, national psychiatric associations and local psychiatric websites. A search was also carried out for review articles, systematic reviews and primary research relating to guidelines and recommendations about schizophrenia treatment, costs and burden of disease, resource utilization, stigmatization and discrimination related to schizophrenia.

RESULTS

Epidemiology of Schizophrenia and Negative Symptoms

Altogether more than 9,000 records from three databases were screened in order to identify relevant studies that fulfilled predefined inclusion criteria. For epidemiological data and guidelines, more than 1050 records were initially identified (including 650 records for country-specific data). This initial search was further refined by the defined filters to identify 14 publications on the epidemiology of schizophrenia [15-28].

The findings confirmed that schizophrenia is a common psychiatric disorder. The mean incidence of schizophrenia reported in the studies varied greatly from 0.04 to 0.58 per 1,000 individuals in a population per year [16, 29], while lifetime prevalence ranged from 0.4% to 1.4% [15, 21]. This variance was explained mainly by differences in the diagnostic criteria used in the studies. Several of the studies included were conducted in the period prior to the publication of standard diagnostic criteria, such as the DSM-IV and ICD-10; (published in 1994 and 1992, respectively). The actual prevalence of schizophrenia is likely to be higher than these figures if undertreated and never-treated cases are taken in to account [29].

Length of illness, which influences prevalence, is determined by several factors, such as life expectancy, excess mortality after disease onset and impact of treatment. The relatively high prevalence of schizophrenia is due to the early age of onset and the chronic recurring disease course. Gender differences in schizophrenia include an earlier age of onset in men, a more severe disease course, and a slightly higher prevalence, with a male to female ratio of 2:1 [15]. However, data relating to gender differences are inconsistent and only some of the study authors agreed that prevalence of schizophrenia is higher in males than in females, while others described the ratio as equal [21]. Full country-specific data on the prevalence and incidence of schizophrenia are shown in Table **1**. No published data for Slovakia and Hungary were available.

Data on the frequency of negative symptoms were limited and inconsistent. The heterogeneity of the published data reflects the use of different definitions and methods for evaluating negative symptoms. Irrespective of these limitations, the published data relating to negative symptoms indicated the following:

- At least one negative symptom was present in 57.6% of patients with schizophrenia and in 50–90% of individuals experiencing their first psychotic episode [5].

- Persistent negative symptoms were experienced by 20–40% of patients with their first psychotic episode [41, 42].

- Primary negative symptoms were observed in 10–30% of patients, with 17.8% of patients experiencing more than one type of negative symptoms [41, 42].

Table 1. **Epidemiological data for seven CEE countries.**

Country and Population in 2012 [Eurostat]	Prevalence	Incidence per 1,000 population per year
Poland Population: 38,538,447	▪ 1% [30] ▪ Estimated number of patients with schizophrenia: 350,000–500,000 [30, 31]	▪ 0.15–0.30 per 1,000 [30]
Slovakia Population: 5,404,322	▪ –	▪ –
Estonia Population: 1,325,217	▪ 6.69 per 1,000 people ▪ Highest in men aged 15–44 years and women aged over 45 [32] ▪ Estimated number of people with diagnosed schizophrenia: 13,000 [33]	▪ Estimated at 0.45–1.30 cases per 1,000 [32, 34]
Serbia Population: 7,216,649	▪ 5.41 per 1,000 patients ▪ Estimated number of patients with schizophrenia: 31,149 [35]	▪ –
Croatia Population: 4,275,984	▪ 3.94–5.1 per 1,000 population [36, 37] ▪ Number of diagnosed patients with schizophrenia registered in primary care: 56,763 [38]	▪ 0.21–0.27 per 1,000 [36, 37] based on ICD-10 criteria
Slovenia Population: 2,055,496	▪ Estimated number of patients with schizophrenia: 19,000 [39] ▪ 10,294–20,588 (prevalence 0.5–1.0%) [40]	▪ 0.15 per 1,000 (range 0.08–0.43) [39] ▪ 0.04–0.22 according to DSM-IV [40] ▪ 0.05-0.23 according to ICD-10 [40]
Hungary Population: 9,931,925	▪ –	▪ –

– Data not identified in search
DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-10= International Classification of Diseases 10th Revision

- The most frequent negative symptoms reported were social withdrawal (45.8%) and emotional withdrawal (39.1%) [5].

Mortality

All mental illnesses are associated with an increased risk of premature death. A substantial number of publications identified here reported higher mortality in people with schizophrenia compared with the general population, with standardized mortality ratios ranging from 2.58 to 4.30 [25, 43].

One reason for the excess mortality in patients with schizophrenia is suicide rate, which is ten times higher among people with mental illness than in the general population [43]. In addition, comorbidities, such as cardiovascular disease, stroke, chronic lung disease and infection are increased in patients with schizophrenia compared with the general population [16, 43]. The most frequently cited reasons for elevated mortality in schizophrenia are outlined in Table **2** [21, 23, 25, 27, 43].

Clinical Practice Guidelines

The literature search identified 11 international, important publications that contained guidelines and recommendations for the treatment of patients with schizophrenia. These are summarized in Table **3**.

Table 2. **Reasons for elevated mortality in schizophrenia.**

Reason	Examples
Direct effect of mental illness or treatment-related adverse effect	Worsening of metabolic profile leading to increased risk of cardiovascular disease
Effect of mental illness on lifestyle and environment/patients' negative attitude towards their physical health	Increased probability of smoking, alcohol use, drug use, physical inactivity, and poor diet – leading to increased risk of cardiovascular disease
Natural causes of death	Cardiovascular disease, stroke, chronic lung disease and infections
Suicide	-

All the identified guidelines recommended pharmacotherapy with either first- or second-generation antipsychotics for the treatment of schizophrenia. However, according to guidelines, pharmacotherapy does not address all aspects of schizophrenia and should always be accompanied by psychosocial intervention. Guidelines indicate that a personalized treatment approach is a key to optimizing therapeutic effect and that givies patients a choice in treatment and encourages patients compliance. Recommendations suggest low doses initially with gradual increases to achieve an optimal

Table 3.   Summary of guidelines identified in the literature search.

Source	Publication year(s)
World Federation of Societies of Biological Psychiatry [44–47]	2005, 2006, 2012, 2013
British Association for Psychopharmacology [48]	2011
National Institute for Health and Care Excellence [29]	2010
The Schizophrenia Patient Outcomes Research Team [49]	2010
American Psychiatric Association [50, 51]	2004, 2009
Royal Australian and New Zealand College of Psychiatrists [52]	2005
Canadian Psychiatric Association [53]	2005
Other key guidelines, e.g. for long-acting injections and negative symptom management [6]	(various)

balance of efficacy and tolerability. The use of antipsychotic therapy and the decision to switch between them, should be clinically justified (for example, by poor compliance, drug intolerance or lack of efficacy). Use of more than one antipsychotic (polytherapy) is not recommended in the guidelines, except for short periods, such as when switching medications.

Second-generation antipsychotics are recommended as first-line therapy and as a treatment option in case of side effects with first-generation antipsychotics. When treating people with a first episode of schizophrenia, antipsychotic medication may be initiated at the lower end of the licensed dosage range. Moreover, treatment with the lowest effective dose is recommended throughout the course of schizophrenia. All available guidelines indicate clozapine for treatment-resistant schizophrenia (defined as the patient not responding adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs, including at least one non-clozapine second-generation antipsychotic). It is important to monitor patients' physical health, with a particular focus on the risk of cardiovascular disease. Several guidelines also indicate that electroconvulsive therapy should be considered for treatment of schizophrenia if clozapine is not effective.

Most of the guidelines recommend that acute schizophrenia episodes should be treated with antipsychotic medication, although they note that antipsychotics are more effective at alleviating positive rather than negative symptoms. Both primary and secondary negative symptoms may present in the course of illness, and distinguishing between them is key for optimal treatment. Possible causes of secondary negative symptoms should be identified and managed as appropriate. The guidelines, in particular the World Federation of Societies of Biological Psychiatry guidelines (WFSBP), state that different treatments and strategies may potentially be needed for comorbid conditions, such as antidepressants for depression, anxiolytics for anxiety disorders, and antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal symptoms. The WFSBP guidelines also note that first-generation antipsychotics are helpful in the treatment of secondary but not primary negative symptoms. Second-generation antipsychotic drugs seem to be superior to first-generation drugs in the treatment of primary negative symptoms, although the relative efficacy of first- and second-generation antipsychotics for the treatment of secondary negative symptoms has not been established in clinical trials [46].

Our literature search indicates that there is insufficient evidence to support treatment recommendations regarding pharmacotherapy for primary or persistent negative symptoms in schizophrenia. Nevertheless, there is a clear need to help patients experiencing negative symptoms. The 2012 WFSBP guidelines recommend two second-generation antipsychotic drugs for the treatment of primary and secondary negative symptoms: olanzapine and amisulpride (Table **4**) [46].

CEE-SPECIFIC GUIDELINES

Local-language CEE-specific schizophrenia treatment guidelines are listed in the Appendix. Importantly, these publications are in agreement with the non-CEE guidelines with respect to the treatment of schizophrenia.

DISCUSSION

Schizophrenia is a prevalent mental health illness and poses a considerable burden on patients and healthcare resources worldwide. The worldwide incidence of schizophrenia reported in this review varies from 0.04 to 0.58 per 1,000 population per year. However, when the diagnosis is made according to DSM or ICD core criteria, and corrected for age, mean incidence is 0.11 (range 0.07–0.17) per 1,000 population per year [16]. Gender differences in schizophrenia include an earlier age of onset in men. Estimates of the lifetime prevalence of schizophrenia range from 0.4% to 1.4%. The early age of onset and the chronic disease course may explain these relatively high figures.

Many publications report higher mortality among individuals with mental illness compared with the general population. Standardised mortality ratios for patients with schizophrenia vary from 2.58 to 4.30. It is known that the suicide rate is increased among patients with schizophrenia; other reasons for the mortality excess include cardiovascular disease, stroke, chronic lung disease and infections [26, 43]. The risk of mortality in patients with schizophrenia may also be affected by demographic, clinical, political (pharmaco-economic) and cultural factors [23]. Patients with schizophrenia may also have limited access to and lower quality of healthcare services compared with the general population. Importantly, adherence to guideline-recommended pharmacotherapy is associated with reduced mortality among patients with schizophrenia [23, 27].

Table 4.   WFSBP 2012 recommendations for treatment of primary and secondary negative symptoms [46].

Antipsychotic agent	Primary negative symptom		Secondary negative symptom	
	Category of evidence	Recommendations	Category of evidence	Recommendations
Amisulpride	**A**	**1**	**A**	**1**
Asenapine	F	-	B	3
Aripiprazole	C3	4	A	1
Clozapine	C3	4	A	1
Haloperidol	F	-	A	1
Iloperidone	F	-	F	-
Lurasidone	F	-	B	3
Olanzapine	**A**	**1**	**A**	**1**
Paliperidone	F	-	A	1
Quetiapine	B	3	A	1
Risperidone	F	-	A	1
Sertindole	F	-	A	1/2
Ziprasidone	B	3	A	1
Zotepine	D	5	A	1

Category of evidence: A: Full evidence from controlled studies; B: Limited positive evidence from controlled studies; C: Evidence from uncontrolled studies or case reports/expert opinion, C1: Uncontrolled studies; C2: Case reports; C3: Evidence is based on the opinion of experts in the field or clinical experience; D: Inconsistent results – positive randomized controlled trials are outweighed by an approximately equal number of negative studies; E: Negative evidence; F: Lack of evidence

Recommendation: Grade1: Category A evidence and good risk–benefit ratio; 2: Category A evidence and moderate risk–benefit ratio; 3: Category B evidence; 4: Category C evidence; 5: Category D evidence.

The guidelines identified in the literature review unanimously state that pharmacotherapy with antipsychotic drugs is the cornerstone of schizophrenia treatment. However, psychotherapy (such as social support, psychoeducation, cognitive behavioural therapy, family intervention, and art therapy) may accompany pharmacotherapy. Guidelines recommend that use of more than one antipsychotic drug should be avoided, except when switching antipsychotic agents or if other treatments have failed.

Guidelines for the treatment of negative symptoms stress the importance of distinguishing between primary negative symptoms and secondary negative symptoms. The treatment of secondary negative symptoms is based on identifying and treating the underlying causes (such as Parkinson's syndrome, major depression or extrapyramidal symptoms). In some cases clozapine alone or in combination with antipsychotics or other medication is recommended. The recently published WFSBP guidelines indicate that two second-generation antipsychotic drugs – olanzapine and amisulpride – may be efficacious in the treatment of primary negative symptoms [46].

The objective of this study was to gather data related to the burden of schizophrenia in seven CEE countries, with a particular focus on negative symptoms. Despite the extensive search, we were unable to find relevant data in all areas of interest. In particular, there was a lack of information regarding socioeconomic status and mortality in patients with schizophrenia in many countries. Consequently, data obtained from the main literature search was supplemented with information from non-CEE countries, such as the WFSBP guidelines. In addition, the data presented in this review are derived from many different types of publications. Epidemiological data were identified in the local literature and extracted from reviews, textbooks, health statistics, national registries and local publications, which makes comparison between sources difficult. Furthermore, many countries do not have their own national guidelines. National guidelines and treatment recommendations for schizophrenia were identified in Hungary, Poland and Croatia and Estonia.

CONCLUSION

This comprehensive review of current literature and guidelines confirms that schizophrenia is a common mental illness that places a substantial burden on the patient and wider society. Guidelines recognize a role for second-generation antipsychotics in the treatment of negative symptoms. However, these findings indicate that there is currently insufficient evidence to support treatment recommendations regarding pharmacotherapy for primary or persistent negative symptoms in schizophrenia. Thus, options for treatment of negative symptoms are limited. This literature review highlights the importance of developing new therapeutic approaches, and exploring novel therapies such as glutamatergic agents, which may be of great value in future treatment strategies. There remains an important unmet clinical need in schizophrenia regarding treatment of negative symptoms, and improvement of overall patient outcomes.

CONFLICT OF INTEREST

No authors had any direct conflict of interest to declare. However, authors who are also employees of Roche could

potentially have a conflict of interest in case Roche develops a product in the schizophrenia area in the future.

ACKNOWLEDGEMENTS

APPENDIX

Guidelines identified in local literature review

Country	Identified guidelines
Croatia	▪ **Štrkalj Ivezić S, Folnegović Šmalc V, Mimica N, Bajs Bjegović M, Makarić G, Bagarić A,** *et al.* (2001). Dijagnostičke I Terapijske Smjernice (Algoritam) Za Liječenje Shizofrenije Preporuke Hrvatskog Društva Za Kliničku Psihijatriju *Hrvatskoga Liječničkog Zbora Liječnički Vjesnik : Glasilo Hrvatskoga Liječničkog Zbora* (0024-3477)**123**:287-338. ▪ **Štrkalj-Ivezić S; Folnegović-Šmalc V** (1999). Terapijski algoritam shizofrenije Urednik/ci: Štrkalj-Ivezić S, Folnegović-Šmalc V Izdavač: Hrvatski Liječnički zbor, Hrvatsko društvo za klin. *Psihijatriju*, 1999. ▪ **Mimica N** (1999). Psihofarmakologija održavanja Terapijski algoritam shizofrenije [Therapeutic algorithm for schizophrenia Psychopharmacology of maintenance] Izvornik: Priručnik za praćenje seminara Terapijski algoritam shizofrenije Dio CC časopisa: NE Skup: *Terapijski algoritam shizofrenije, Zagreb, Republika Hrvatska*. **10**:22.-23.
Estonia	▪ **Kleinberg A, Poolamets P, Hüva K, Tänna K, Jaanson P**. Eesti Psühhiaatrite Selts. Skisofreenia ravijuhis. 2000. Published online http://www.kliinikum.ee/psyhhiaatriakliinik/lisad/rav i/ps-ravi/SCH/skisofreenia_ravijuhis.htm. Accessed 17 April 2014.
Hungary*	▪ **Herold R** (2012). A szkizofrénia hosszú távú kezelése *Orvosi Hetilap*. **153**:1007-12. ▪ **Fekete S, Herold R, Tényi T, Trixler M**. Szkizofrénia szakmai protokoll, *Pszichiátriai útmutató, 2010*. ▪ **Pszichiátriai Szakmai Kollégium**. Skizofrénia szakmai protokoll: az Egészségügyi Minisztérium szakmai protokollja Útmutató. *Klinikai Irányelvek Kézikönyve-Pszichiátria, 2008*. ▪ **Bitter I., Jermendy Gy** (2005). Antipszichotikus terápia és metabolikus szindróma - A Magyar Diabe-

	tes Társaság Metabolikus Munkacsoportja és a Pszichiátriai Szakmai Kollégium konszenzus-értekezlete Psychiatria Hungarica.**20**:312-5. ▪ **Bitter I** (2004). A szkizofrénia modern gyógyszeres kezelése *Orvosi Hetilap*, **145**:105-9. ▪ **Palik É** (2002). Antipszichotikum-kezelés hatása a szénhidrát anyagcserére *Családorvosi Fórum*.**9**:14-6. ▪ **Hungarian College of Neuropsychopharmacology** (1999)**.** *Antipszichotikumok alkalmazása Psychiatria Hungarica*.**5**:584-604. ▪ **Antipszichotikumok Konszenzus Konferencia** (2002): Hungarian College of Neuropsychopharmacology, Magyar Pszichofarmakológiai Társaság, Magyar Pszichiátriai Társaság Antipszichotikumok alkalmazása *Neuropsychopharmacologia Hungarica*.**4**:115-21. ▪ **Arató M, Bánki MCs, BartkóGy, Bitter I, Borvendég J, Janka Z,** *et al.* (1996). *Antipszichotikumok Konszenzus Konferencia Psychiatria Hungarica*.**6**:717-20.
Poland	▪ **Jarema M** (2012). Zalecenia w sprawie stosowania leków przeciwpsychotycznych II generacji [Recommendations for the use of second generation antipsychotics]; *Farmakoterapia w psychiatrii i neurologii*. 51-7. ▪ **Jarema M** (2008). Zalecenia w sprawie stosowania leków przeciwpsychotycznych II generacji. *Psychiatria Polska*. 2008;6:969-77. ▪ **Jarema M, Rabe-Jabłońska J**. Psychiatria. Podręcznik dla studentów medycyny; Wydawnictwo lekarskie PZWL, Warszawa 2011 ▪ **Kiejna A, Landowski J** *et al.* (2006). Standardy leczenia farmakologicznego schizofrenii [Pharmacological standards in schizophrenia treatment] *Psychiatria Polska* **40**:1171-205.
Serbia	▪ **Jašović-Gašić M, Damjanović A, Lečić Toševski D, Đukić-Dejanović S, Vukić-Drezgić S**. Terapijske smernice za lečenje shizofrenije [Therapeutic guidelines for treatment of schizophrenia]; Published by: Psychiatric branch of Serbian Medical Society, Printed by: Grafolik (not indexed by National Library of Serbia), 2008
Slovakia	▪ **Vavrušová L., Kořínková V., Pečeňák J., Korcsog P., Janoška D.;** Racionálna liečba antipsychotikami [Rational treatment with antipsychotics]; Methodical letter of Central Committee for Rational Pharmacotherapy and Drug Policy of Ministry of Health of Slovak Republic, 2003
Slovenia	▪ **Kores-Plesničar Blanka**. Osnove psihofarmakoterapije. booklet 2006

*Guidelines and recommendations

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