ASSOCIATIONS BETWEEN NEGATIVE SYMPTOMS, SERVICE USE PATTERNS, AND COSTS IN PATIENTS WITH SCHIZOPHRENIA IN FIVE EUROPEAN COUNTRIES

Martin Knapp, Paul McCrone, Oscar Leeuwenkamp

Abstract

Object: Negative symptoms in patients with schizophrenia can adversely affect functionality and social interactions. However, the impact of negative symptoms on schizophrenia-related healthcare costs has not been well studied. We sought to examine this relationship in a European sample.

Method: Data from the European Psychiatric Services: Inputs Linked to Outcome Domains and Needs (EPSILON) study (1998) were analysed. Using scores obtained on relevant items from the Brief Psychiatric Rating Scale, three measures of negative symptoms were generated for analysis: (1) a binary variable indicating the presence or absence of negative symptoms, (2) a negative symptom score reflecting the symptom severity, and (3) a negative symptom component score. Multiple regression models were used to analyse the impact of negative symptoms on the use and costs of inpatient, outpatient, and community-based services. Results are controlled for age, sex, marital status, employment status, race, education, psychiatric history, and study centre.

Results: The sample comprised 404 patients from five study centres (Amsterdam, Copenhagen, London, Santander, Verona). Mean age was 41; 57% were men, 65% were single, 85% were white, 69% were living alone or with relatives, and 70% were unemployed or on a pension. Negative symptoms were present in 247 patients (61%), with the lowest incidence in Verona (49%) and the highest in Amsterdam (79%). Unadjusted data from all sites showed that negative symptoms were associated with higher total costs and costs for inpatient, day care, residential care, and community services, but with lower costs for outpatient care. After adjusting for sociodemographic and clinical variables, the only statistically significant correlation was higher total costs in patients with negative symptoms. Patterns of costs and resource use varied across and within study sites.

Conclusions: Negative symptoms are associated with increased inpatient and total costs, and decreased outpatient costs. Therefore, allocating resources for the improved management of negative symptoms may reduce the overall costs of schizophrenia care. Further research would help to determine how differences in schizophrenia management between countries influenced patterns of cost associations with patient characteristics.

Key Words: Negative Symptoms – Schizophrenia – Service Use Pattern – Cost

Declaration of interest: Professor Martin Knapp has received grant funding from Bristol Myers Squibb Pharmaceuticals Limited and from Eli Lilly

Martin Knapp, PhD,[1,2] Paul McCrone, PhD,[2] Oscar Leeuwenkamp, PhD[3]
[1] Personal Social Services Research Unit, London School of Economics; [2]Centre for the Economics of Mental Health, Institute of Psychiatry, King's College London, UK; [3]Organon, a part of Schering-Plough Corporation, Oss, The Netherlands

Corresponding Author
Martin Knapp, PhD, Centre for the Economics of Mental Health, Institute of Psychiatry, King's College London 16 De Crespigny Park, London SE5 8AF, UK - Phone: 44 20 7848 0174 - Fax: 44 20 7701 7600
E-mail: Martin.Knapp@iop.kcl.ac.uk

Introduction

People with schizophrenia exhibit a combination of positive, negative, cognitive, and affective symptoms. Positive symptoms (such as delusions, disorganized speech, and grossly disorganised or catatonic behavior) are overt manifestations of the illness, whereas negative symptoms (such as alogia, avolition, and anhedonia) manifest as a lack of normal behavior (American Psychiatric Association 2000). Patients with negative symptoms tend to become socially withdrawn and have little emotional expressivity.

Schizophrenia raises many challenges, with patients requiring long-term treatment and support, and generally using many health care and other services. High-income countries typically spend up to 3% of their total health care expenditures on schizophrenia care (Evers and Ament 1995, Knapp et al. 2004, Oliva-Moreno et al. 2006). Apart from often substantial direct costs of treatment, especially associated with hospitalisation, the indirect costs associated with lost productivity, unemployment and impacts on the family can contribute more than half the overall costs of the disorder (Hu 2006, Mangalore and Knapp 2007). These

Submitted February 2008, Accepted November 2008

© 2008 Giovanni Fioriti Editore s.r.l.

economic impacts of schizophrenia vary considerably across countries, because of differences in service systems, entitlements to subsidised treatment, labour market conditions and cultural circumstances influencing the expected roles of families. Consequently, the direct costs of schizophrenia treatment can account for anywhere from 30% (Canada, Hungary, Italy, and Norway) to 50% (US, UK, Spain) of the total costs of schizophrenia treatment (Davies and Drummond 1994, Hu 2006, Mangalore and Knapp 2007, Oliva-Moreno et al. 2006, Rice and Miller 1998).

Although data directly comparing the impact of negative symptoms on economic outcomes are limited, there is evidence to suggest that negative symptoms and their severity increase the cost of treatment. In one study, a cluster analysis that identified patients with similar profiles of schizophrenia symptoms found that monthly treatment costs were higher when predominant negative symptoms were present compared with low or moderate negative symptoms (Mohr et al. 2004). It has also been reported that the costs of psychiatric care are highly correlated with social disability, which is in turn highly correlated with negative symptoms (Steinert et al. 1999).

Given the scarcity of health care and other resources, decision-makers are looking for information that can help them to understand the characteristics of patients - especially their symptoms and associated needs - that influence the costs of treatment and support. The goal of the present study was to examine whether there was an association between direct costs and the symptom profiles of people with schizophrenia. In particular, and as suggested by earlier studies (Mohr et al. 2004, Steinert et al. 1999), it was hypothesised that there would be a positive association between direct medical costs and negative symptoms.

Methods

Data source

Data were drawn from the European Psychiatric Services: Inputs Linked to Outcome Domains and Needs (EPSILON) study. The EPSILON study was conducted between 1996 and 2000 at 5 European sites (Amsterdam, The Netherlands; Copenhagen, Denmark; London, England; Santander, Spain; and Verona, Italy) with funding from the European Commission. Its aim was to develop standardized instruments that would facilitate future cross-national research (Becker et al. 1999, Becker et al. 2000). The variability between sites in the systems of mental health care was seen as a benefit in this respect (Becker et al. 2000).

The data analyzed were collected from and about patients aged 18 to 65 who had an International Classification of Diseases (ICD-10) diagnosis of schizophrenia and had received mental health services within the preceding 3 months. Patients who were currently in forensic settings or who had been in inpatient care ≥ 1 year were excluded to avoid bias-associated differences in long-term institutional care across countries and to focus the study on current active care by mental health services.

Measurement of negative symptoms

The expanded version of the Brief Psychiatric Rating Scale (BPRS) was used to measure symptoms (Lukoff et al. 1986). It contains 22 items relating to specific symptoms, which are rated by physicians as 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, or 7 = extremely severe. The BPRS contains 4 items that clearly relate to negative symptoms: item 13 (self-neglect), item 16 (blunted affect), item 17 (emotional withdrawal), and item 18 (motor retardation).

Using the BPRS, three measures of negative symptoms were developed: a binary variable indicating the presence of any of the above BPRS negative symptom items, a severity index based on the mean score of these individual BPRS negative symptom items, and a severity index based on a principal-components analysis of the individual BPRS items. In a similar way to Ruggeri et al. (2005), who had previously investigated the factor structure of the BPRS, four components were extracted and then rotated using the varimax method to aid interpretation. Component 4 (**Appendix**), which included blunted affect, emotional withdrawal, and motor retardation, was related to negative symptoms. The components are not the same as those produced by Ruggeri et al., for example the item "self-neglect" did not appear in Component 4. The BPRS also allowed us to generate principal component scores for positive symptoms, mania and anxiety/depression. In addition, we computed average scores (higher scores indicating more symptoms) for negative symptoms, positive symptoms, cognition (for which a principal components score was not generated), mania and anxiety/depression; and also variables simply indicating whether these symptoms were present or not.

Measurement of service use and costs

The Client Sociodemographic and Service Receipt Inventory, adapted from an earlier instrument for use in the EPSILON study (Chisholm et al. 2000), was employed to assess service use and costs. Service costs were estimated by combining service use data with local unit costs. These service costs were converted to 1998 British pound (£s) levels using purchasing power parity rates. These calculations have previously been described (Knapp et al. 2002).

Data analytic procedures

The impact of negative symptoms on service costs (inpatient care, outpatient care, day care, community services, residential care, all services) was assessed using two types of regression model for each measure of negative symptoms. First, the ordinary least squares method was used. Because of the non-normal distribution of the regression residuals, bootstrapping was used to generate 95% confidence intervals around the regression coefficients. Second, generalised linear models (GLM) with log links and gamma distributions (to reflect the skew in the cost distributions) were used. In addition, logistic regression analyses were conducted

to assess the impact of each negative symptom index on the proportion of people using inpatient care, outpatient care, and community services.

To control for sociodemographic and clinical characteristics, as well as negative symptoms, we followed the methods described by Knapp et al. (2002) in their earlier investigation of the EPSILON dataset and included the following variables in the regression models (asterisk denotes indicator variables): centre 2 (Copenhagen)*, centre 3 (London)*,centre 4 (Santander)*, centre 5 (Verona)*, age, male sex*, married*, nonwhite ethnic group*, minority first language*, years of education, employed*, and number of previous admissions. The models included variables relating to (i) the presence of other symptoms (positive symptoms, cognition, mania and anxiety/depression), (ii) the mean level of these symptoms, or (iii) the other three component scores from the principal components analysis. We also included in subsequent analyses variables relating to functioning, quality of life, needs and satisfaction based on the Global Assessment of Functioning (Endicott et al. 1976), the Lancashire Quality of Life Profile (Oliver et al. 1997), the Camberwell Assessment of Need (Phelan et al. 1995) and the Verona Service Satisfaction Scale (Ruggeri and Dall'Agnola 1993) respectively. Finally, we estimated regression models that included a variable reflecting the interaction between negative and cognitive symptoms.

Results

Differences in the background characteristics of the patient sample between sites are presented in **Table 1**. At least one negative symptom was present in 61% of the population (**Table 2**). Verona had the lowest rate of negative symptoms (49%) and the lowest negative symptom severity, as indexed by both mean negative symptom (1.41) and component (-0.26) scores. The highest rate of negative symptoms was reported in Amsterdam (79%), but the highest mean negative symptom (1.84) and component (0.31) scores were found in Santander.

Unadjusted relationship between negative symptoms and service costs

The unadjusted mean annual costs (i.e., costs without adjustment for background or clinical characteristics) for patients with and without negative symptoms are presented in **Table 3**. Mean annual costs were 48% to 180% higher for patients with negative symptoms in all categories, except for outpatient care where costs were 42% lower for patients with negative symptoms.

Relationship adjusted for background characteristics (OLS model)

After adjusting for background characteristics, patients with negative symptoms continued to show trends toward higher direct costs for service use, but the only significant difference was for total costs, which on average were £2609 higher than if negative symptoms were not present (**Table 4**). When the mean negative symptom score was included in the model, inpatient and total costs were found to increase with symptom severity. When negative symptom severity was measured using

Table 1. *Background Characteristics by Study Centre*

		Amsterdam (n=61)	Copenhagen (n=52)	London (n=84)	Santander (n=100)	Verona (n=107)	All Sites (N=404)	*P* Value
Percentage of Population								
Sex (%)	Men	67.2	59.6	58.3	59.0	48.6	57.4	0.197
	Women	32.8	40.4	41.7	41.0	51.4	42.6	
Marital status	Single	72.1	59.6	64.3	71.0	57.9	64.9	
	Married	9.8	11.5	15.5	16.0	24.3	16.6	0.102
	Other	18.0	28.8	20.2	13.0	17.8	18.6	
Ethnicity	White European	54.1	92.3	65.5	100.0	100.0	84.9	<0.001
	Other	45.9	7.7	34.5	0.0	0.0	15.1	
Language	National language	78.7	88.5	92.9	98.0	100.0	93.3	<0.001
	Other language	21.3	11.5	7.1	2.0	0.0	6.7	
Living situation	Alone	49.2	65.4	41.7	7.0	15.0	30.2	
	With partner	8.2	11.5	16.7	17.0	25.2	17.1	<0.001
	With relatives	19.7	3.8	20.2	72.0	49.5	38.6	
	With others	23.0	19.2	21.4	4.0	10.3	14.1	
Accommodation	Domestic	70.5	80.8	79.8	100.0	91.6	86.6	
	Community	27.9	15.4	13.1	0.0	7.5	10.9	<0.001
	Other	1.6	3.8	7.2	0.0	0.9	2.4	
Occupation	Employed/student	18.0	15.4	4.8	20.0	23.4	16.8	
	Sheltered work	8.2	3.8	1.2	2.0	4.7	3.7	<0.001
	Unemployed/pension	57.4	80.8	91.7	65.0	57.9	69.6	
	Housewife/husband	16.4	0.0	2.4	13.0	14.0	9.9	
State benefits	Yes	93.4	100.0	91.7	74.0	35.5	73.8	<0.001
	No	6.6	0.0	8.3	26.0	64.5	26.2	
Income source	Salary/wage	11.5	2.1	2.4	13.3	23.1	11.9	
	Benefits	85.2	97.9	89.3	46.9	25.0	62.2	<0.001
	Family	3.3	0.0	7.1	39.8	28.8	19.5	
	Other	0.0	0.0	1.2	0.0	23.1	6.3	
Mean (standard deviation)								
Age (y)		39.9 (9.9)	39.4 (9.6)	43.8 (12.3)	39.9 (9.3)	43.0 (12.4)	41.8 (11.1)	0.024
General education (y)		11.8 (2.2)	9.9 (2.3)	11.3 (1.5)	10.7 (2.3)	8.7 (3.2)	10.4 (2.7)	<0.001
GAF score		56.48 (11.91)	53.57 (14.32)	58.71 (11.11)	58.97 (18.82)	56.64 (16.57)	57.3 (15.3)	0.273
BPRS score		1.65 (0.47)	1.67 (0.49)	1.51 (0.43)	1.60 (0.52)	1.47 (0.46)	1.56 (0.48)	0.047

Table 2. *Measures of Negative Symptoms by Study Centre*

	Presence of Negative Symptoms*, n (%)	Negative Symptom Score*, mean (SD)	Negative Symptom Component Score*, mean (SD)
Amsterdam (n=61[a])	48 (79)	1.72 (0.72)	–0.06 (0.89)
Copenhagen (n=52[a])	31 (60)	1.78 (0.88)	0.02 (1.30)
London (n=84[a])	50 (60)	1.57 (0.69)	–0.05 (0.71)
Santander[†] (n=100[a])	69 (69)	1.84 (0.99)	0.31 (1.22)
Verona (n=107[a])	52 (49)	1.41 (0.66)	–0.26 (0.76)
All sites (n=404[a])	250 (62)	1.64 (0.81)	0.00 (1.00)

SD=standard deviation.
**P*=0.002 for all comparisons between sites. Chi- square test was used for the binary variable (presence of negative symptoms); analysis of variance was used for continuous variables (negative symptom score and negative symptom component score). *P* value is the same for all comparisons because the measures were strongly correlated.
[†]A Bonferroni test for negative symptom score and negative symptom component score revealed that the key difference was between Verona and Santander.
[a]These are the total sample sizes at each site rather than the sample for whom negative symptom scores could be computed. The total sample was 403 for the presence of negative symptoms, 397 for the negative symptom score and 378 for the component score. The numbers by site are available from the authors.

Table 3. *Unadjusted Impact of Negative Symptoms on Mean (SD) Service Costs (£ at 1998 Price Levels)*

Service	Negative symptoms absent (n=153)	Negative symptoms present (n=250)	95% CI of difference
Inpatient	1986 (9334)	3340 (12084)	-809 to 3328
Outpatient	386 (1291)	223 (530)	-400 to 18
Day care	618 (1723)	1334 (3665)	200 to 1300
Community services	387 (1022)	573 (1453)	-59 to 439
Residential care	177 (767)	496 (1460)	87 to 537
Total	3555 (9945)	5966 (12809)	152 to 4663

the component score, only total costs were significantly increased in patients with negative symptoms.

After adjusting for background characteristics, analysis within centres revealed country-specific cost patterns (**Table 4**). In London, the presence of negative symptoms and the mean symptom score was associated with increased inpatient and total costs, and the component score was significantly associated with increased total costs. In Verona, the presence of negative symptoms was related to higher day care costs, the mean negative symptom score was associated with higher inpatient and total costs and the component score was associated with higher outpatient and total costs. In Santander, the component score was inversely related to outpatient costs. There were no significant relationships between negative symptoms and costs in Amsterdam or Copenhagen.

Table 4. *Impact of the Presence of Negative Symptoms, Mean BPRS Score, and BPRS Component Score on Service Costs (£, at 1998 Price Levels) Adjusted for Background Characteristics Using Ordinary Least Squares Linear Regression Model*

	Mean Cost Differences (£) for Patients With Versus Without Negative Symptoms (Bootstrapped 95% CIs)					
	Inpatient	**Outpatient**	**Day Care**	**Community Services**	**Residential Care**	**All Services**
Pooled sample						
Presence (n=384)	2118 (–90 to 4205)	–186 (–438 to 41)	436 (–136 to 1054)	155 (–87 to 432)	84 (–164 to 324)	2609 (244 to 4935)*
Mean score (n=385)	1950 (236 to 3861)*	–44 (–165 to 55)	239 (–305 to 986)	69 (–39 to 199)	–25 (–193 to 118)	2188 (555 to 4212)*
Component score (n=368)	988 (–187 to 2292)	–36 (–126 to 36)	268 (–133 to 851)	74 (–13 to 201)	43 (–64 to 154)	1337 (103 to 2734)*
Amsterdam						
Presence (n=59)	214 (–2701 to 3017)	–226 (–979 to 566)	–999 (–3309 to 1379)	230 (–264 to 887)	476 (–238 to 1252)	–305 (–4583 to 3232)
Mean score (n=59)	2376 (0 to 5112)	–54 (–427 to 476)	–782 (–1680 to 545)	59 (–186 to 598)	131 (–180 to 577)	1729 (–1215 to 4675)
Component score (n=59)	2275 (0 to 4535)	–139 (–481 to 182)	–798 (–1524 to 183)	47 (–172 to 345)	145 (–126 to 571)	1530 (–970 to 3786)
Copenhagen						
Presence (n=47)	10,546 (–1944 to 26775)	–501 (–1817 to 380)	284 (–1336 to 1443)	96 (–400 to 795)	–397 (–1220 to 342)	10,028 (–3653 to 25986)
Mean score (n=47)	5585 (–5207 to 17600)	–338 (–1429 to 730)	–175 (–1336 to 1062)	342 (–40 to 1007)	182 (–438 to 652)	5595 (–5100 to 18252)
Component score (n=42)	129 (–5333 to 5624)	–146 (–835 to 421)	19 (–457 to 785)	169 (–81 to 641)	122 (–261 to 393)	293 (–5365 to 6258)
London						
Presence (n=79)	5630 (844 to 11840)*	–106 (–406 to 183)	21 (–1319 to 1529)	–8 (–651 to 643)	279 (–717 to 1335)	5816 (596 to 12457)*
Mean score (n=80)	8316 (965 to 16205)*	–118 (–392 to 106)	799 (–469 to 2899)	304 (–241 to 1137)	–499 (–1293 to 358)	8802 (1530 to 16653)*
Component score (n=76)	5724 (–824 to 13784)	–75 (–275 to 54)	929 (–161 to 2589)	263 (–211 to 1030)	–242 (–961 to 724)	6598 (179 to 14860)*
Santander						
Presence (n=100)	–1320 (–3470 to 1056)	–4 (–15 to 5)	NA	42 (–50 to 164)	NA	–1282 (–3450 to 1000)
Mean score (n=100)	–492 (–1685 to 435)	–6 (–17 to 1)	NA	–19 (–73 to 30)	NA	–517 (–1804 to 368)
Component score (n=100)	–559 (–1454 to 236)	–4 (–11 to -0.2)*	NA	–14 (–44 to 16)	NA	–577 (–1429 to 192)
Verona						
Presence (n=99)	1752 (–2908 to 6406)	55 (–207 to 308)	1880 (105 to 3783) *	543 (–214 to 1428)	3 (–335 to 416)	4233 (–1053 to 9198)
Mean score (n=99)	3569 (208 to 8207)*	235 (–33 to 526)	2629 (–134 to 5314)	272 (–169 to 1065)	–119 (–838 to 320)	6586 (2267 to 11220)*
Component score (n=91)	1686 (–704 to 4606)	232 (13 to 418)*	2289 (–449 to 4400)	191 (–142 to 723)	211 (–14 to 633)	4609 (826 to 6535)*

BPRS=Brief Psychiatric Rating Score; NA=not applicable (service was not used).
*$P<0.05$

Table 5. *Impact of the Presence of Negative Symptoms, Mean BPRS Score, and BPRS Component Score on Service Costs (£, at 1998 Price Levels) Adjusted for Background Characteristics and Clinical Variables (Needs, Satisfaction, Quality of Life and Functioning) Using Ordinary*

	Mean Cost Differences (£) for Patients With Versus Without Negative Symptoms (Bootstrapped 95% CIs)					
	Inpatient	**Outpatient**	**Day Care**	**Community Services**	**Residential Care**	**All Services**
Pooled sample						
Presence (n=373)	2140 (328 to 4202)*	-173 (-404 to 30)	250 (-394 to 952)	116 (-139 to 377)	4 (-281 to 260)	2337 (252 to 4596)*
Mean score (n=375)	1761 (-123 to 3757)	-28 (-122 to 67)	115 (-469 to 844)	-1 (-121 to 140)	-128 (-331 to 63)	1720 (-103 to 3778)
Component score (n=358)	796 (-549 to 2246)	-1 (-65 to 69)	134 (-408 to 696)	1 (-111 to 130)	-11 (-162 to 153)	919 (-481 to 2526)
Amsterdam						
Presence (n=56)	341 (-3189 to 5043)	-269 (-918 to 243)	-872 (-3505 to 1212)	3 (-1029 to 690)	216 (-558 to 894)	-581 (-6028 to 4418)
Mean score (n=56)	3099 (0 to 7073)	-102 (-410 to 185)	-897 (-2322 to 534)	-156 (-866 to 537)	26 (-397 to 553)	1970 (-2594 to 5970)
Component score (n=56)	3015 (0 to 5585)	-100 (-433 to 119)	-824 (-1970 to 745)	-170 (-794 to 197)	16 (-355 to 466)	1937 (-2326 to 4843)
Copenhagen						
Presence (n=45)	3822 (-13777 to 24620)	-473 (-2738 to 934)	-315 (-2795 to 1551)	139 (-717 to 1277)	-490 (-1472 to 500)	2683 (-14604 to 25156)
Mean score (n=45)	2056 (-13513 to 19671)	-402 (-2187 to 1291)	-725 (-2067 to 908)	356 (-236 to 1449)	218 (-722 to 916)	1503 (-13459 to 17898)
Component score (n=40)	-3501 (-15004 to 8991)	-67 (-940 to 788)	-208 (-1102 to 837)	141 (-279 to 1003)	152 (-446 to 730)	-3482 (-13206 to 7422)
London						
Presence (n=79)	6451 (1575 to 12346)*	-114 (-439 to 182)	28 (-1641 to 1629)	129 (-491 to 832)	404 (-769 to 1423)	6899 (1054 to 13061)*
Mean score (n=80)	7828 (1486 to 14723)*	-129 (-425 to 125)	1069 (-672 to 3376)	466 (-153 to 1409)	-323 (-1191 to 606)	8911 (2796 to 16380)*
Component score (n=76)	6004 (729 to 12407)*	-78 (-335 to 80)	1300 (-290 to 3390)	455 (-195 to 1586)	-8 (-866 to 934)	7674 (2387 to 13831)*
Santander						
Presence (n=100)	-1625 (-4373 to 1314)	-4 (-15 to 4)	NA	69 (-65 to 252)	NA	-1560 (-4220 to 1568)
Mean score (n=100)	-543 (-1822 to 1055)	-5 (-15 to 3)	NA	-22 (-77 to 31)	NA	-570 (-1781 to 963)
Component score (n=100)	-667 (-1459 to 240)	-3 (-10 to 1)	NA	-15 (-45 to 28)	NA	-684 (-1581 to 302)
Verona						
Presence (n=93)	3484 (-1628 to 8713)	38 (-295 to 316)	1455 (-812 to 3827)	504 (-267 to 1322)	-102 (-547 to 393)	5378 (-356 to 10683)
Mean score (n=94)	3853 (220 to 8602)*	213 (-58 to 514)	1943 (-1049 to 4295)	94 (-455 to 899)	-278 (-1192 to 291)	5824 (978 to 10864)*
Component score (n=86)	2398 (-1326 to 5469)	195 (-96 to 421)	1546 (-1482 to 3529)	-80 (-669 to 639)	52 (-375 to 508)	4111 (-1257 to 6850)

BPRS=Brief Psychiatric Rating Score; NA=not applicable (service was not used).
*$P<0.05$

Relationship adjusted for background and clinical characteristics (OLS model)

After adjusting for background and also clinical characteristics, the presence of negative symptoms was significantly associated with increased inpatient and total costs in the pooled sample (**Table 5**). In London, all negative symptom measures were significantly associated with inpatient and total costs. In Verona, the mean negative symptom score was significantly associated with inpatient and total costs.

Relationship adjusted for background characteristics (GLM)

Adjusting for background characteristics using the GLM, a significant positive relationship was observed between the mean negative symptom score and inpatient costs (**Table 6**). Significant inverse relationships were also observed between mean negative symptom and component scores with outpatient costs. GLM analysis at the level of individual centres was not possible because of instability in the estimates.

Relationship adjusted for background and clinical characteristics (GLM)

After adjustment for background and clinical characteristics, GLM analyses demonstrated that outpatient costs were inversely related to the mean negative symptom and component scores and that mean negative symptom score was inversely related to day care costs (**Table 6**).

Relationship between negative symptoms and use of services

The logistic models that excluded clinical variables (other than the symptom scores) showed that negative symptoms were not related to whether or not patients used specific services (**Table 5**). When functioning, quality of life, needs and satisfaction were included, a significant inverse relationship was observed between the use of outpatient services and both the negative symptom score and the component score. The negative symptom score was also inversely related to the use of day care services (details available from the authors).

Impact of interaction between negative symptoms and cognition on service use and costs

In the OLS model both cognitive and negative symptoms were associated with higher total costs, but the difference was smaller if these symptom types were correlated. At the centre level, the interaction between negative and cognitive symptoms was significant in Verona only. Both these symptoms were significantly associated with lower outpatient costs in Amsterdam, but the cost difference was smaller if the symptom types were correlated. In the GLM model, the interaction between the presence of cognitive and negative symptoms was significantly associated with lower outpatient costs across the pooled sample. Finally, from the logistic models it was observed that the interaction between cognitive and negative symptom scores was positively associated with the use of residential care (details available from the authors).

Discussion

Service use and costs of schizophrenia care from the EPSILON study have been previously reported (Knapp et al. 2002), but that earlier study had not investigated the impact of symptom dimensions on resource use or costs. In the present study, several indices of negative symptoms were found to be associated with the direct costs of treatment. Higher inpatient and total costs, along with lower outpatient costs, were most often associated with negative symptoms. In the pooled sample and with adjustment made for background and clinical characteristics, the presence of negative symptoms resulted in inpatient costs that were £2140 higher than if negative symptoms were absent. This translated to a difference of approximately 11 inpatient days. In the pooled analysis without adjusting for background characteristics, each unit increase in the negative symptom score was associated with increased inpatient costs of £1950 - equivalent to around 10 days. These increases in inpatient days are of both clinical and economic importance.

A possible explanation for decreased outpatient costs could be that patients not experiencing acute positive symptoms might be considered relatively stable, and, therefore, the need for outpatient care or medical attention might be under-recognised in these patients (Dixon et al. 2001). A second possible explanation is that patients who spend more time as inpatients will not have the opportunity or need to use outpatient services. A third consideration is that the negative syndrome could lead to a lower attendance rate for offered outpatient appointments.

Taken together, our findings are generally supportive of the limited number of studies that have indicated that the severity of negative symptoms can increase the costs of schizophrenia treatment (Mohr et al. 2004, Steinert et al. 1999). It should be noted, however, that negative symptoms may be a hallmark of a subtype of schizophrenia with a more insidious onset and worse prognosis.

As in our present study, site-specific differences in clinical characteristics, service use, and costs have previously been observed. For example, during the EPSILON study, about 12% of patients had an inpatient admission, but this rate ranged from 2% to 23% across centres (Knapp et al. 2002). In the present study, at least one negative symptom was present in 61% of patients, and the mean BPRS item negative symptom score was 1.64. However, the incidence of negative symptoms ranged from 49% in Verona to 79% in Amsterdam, and symptom severity scores ranged from 1.41 in Verona to 1.84 in Santander. In terms of costs, even though statistical significance was only achieved in London and Verona, common trends toward higher inpatient and total

Table 6. *Impact of Negative Symptoms on Service Costs Adjusted for (A) Background Characteristics and (B) Background and Clinical Characteristics in the Pooled Sample Using a Generalized Linear Model With Log Link and Gamma Distribution*

	Regression Coefficients for Negative Symptoms (95% CIs)					
	Inpatient	**Outpatient**	**Day Care**	**Community Services**	**Residential Care**	**All Services**
A: Adjustment for background characteristics						
Present (n=384)	–1.17 (–3.56 to 1.21)	–0.71 (–1.55 to 0.12)	–0.02 (–0.70 to 0.66)	0.35 (–0.11 to 0.81)	2.76 (–0.54 to 6.07)	0.16 (–0.51 to 0.83)
Mean score (n=385)	4.49 (0.56 to 8.42)*	–0.78 (–1.32 to –0.24)*	0.22 (–0.20 to 0.65)	0.14 (–0.18 to 0.46)	0.15 (–0.80 to 1.10)	0.23 (–0.19 to 0.65)
Component score (n=368)	2.79 (–2.16 to 7.74)	–0.60 (–0.97 to –0.23)*	–0.08 (–0.40 to 0.24)	0.09 (–0.14 to 0.32)	0.15 (–0.56 to 0.86)	0.17 (–0.16 to 0.50)
B: Adjustment for background and clinical characteristics						
Present (n=373)	7.49 (-5.68 to 20.67)	-0.50 (-1.21 to 0.22)	0.22 (-0.69 to 1.13)	0.23 (-0.22 to 0.68)	-0.33 (-0.20 to 19.48)	0.43 (-0.13 to 0.99)
Mean score (n=385)	6.76 (-3.82 to 17.35)	-1.22 (-1.97 to -0.47)*	-0.79 (-1.37 to -0.21)*	-0.05 (-0.36 to 0.27)	-0.02 (-5.65 to 5.60)	0.10 (-0.32 to 0.52)
Component score (n=358)	5.87 (-12.24 to 23.99)	-0.64 (-1.12 to -0.17)*	-0.07 (-0.47 to 0.34)	-0.06 (-0.29 to 0.18)	-1.37 (-26.74 to 23.99)	-0.02 (-0.37 to 0.33)

*$P<0.05$

Table 7. *Impact of Negative Symptoms on Service Use Adjusted for Background Characteristics in the Pooled Sample Using a Logistic Regression Model*

	Odds Ratios (95% CIs)				
	Inpatient	**Outpatient**	**Day Care**	**Community Services**	**Residential Care**
Present (n=384)	1.27 (0.60 to 2.70)	1.02 (0.55 to 1.89)	0.76 (0.41 to 1.39)	1.41 (0.69 to 2.90)	1.28 (0.51 to 3.22)
Mean score (n=385)	1.24 (0.75 to 2.04)	0.72 (0.47 to 1.11)	0.85 (0.55 to 1.31)	1.18 (0.72 to 1.92)	1.17 (0.69 to 1.97)
Component score (n=368)	0.92 (0.64 to 1.34)	0.72 (0.51 to 1.01)*	0.87 (0.61 to 1.23)	0.94 (0.67 to 1.33)	1.37 (0.91 to 2.04)

Only regression coefficients for the negative symptoms are shown. Sample for day care and residential care excludes Santander, where these services were not used.

*$P<0.05$

costs were generally observed in patients with negative symptoms across centres, with the exception of Santander. These trends may not have reached statistical significance in each study centre because of the relatively small patient samples. It is helpful to recognise that the provision of care varied substantially across sites (Becker et al. 2000). For example, it is commonly thought there is less reliance on inpatient care in Italy than elsewhere, which makes the lower level of negative symptoms in Verona all the more interesting. However, in this study the use of inpatient care in Verona did not differ noticeably from other sites (Knapp et al. 2002). In Santander there was less provision of day care and residential care use compared to other sites. It is difficult to see though whether such differences in services can explain differences in the relationship between negative symptoms and costs.

In these analyses, three negative symptom measures were used: a binary variable indicating the presence or absence of negative symptoms and two indices of symptom severity (mean BPRS item negative symptom score and a component score from principal-components analysis). Because research in this area has rarely been conducted, we used a variety of measures of negative symptoms. Similarly, we have explored associations with costs using a both OLS and GLM estimation methods. There is no consensus as to which is more appropriate, although if the aim is to explain the nature of the relationships rather than to predict costs then the GLM approach may have advantages (Dunn et al. 2003). Most of the associations between these measures and direct costs were not statistically significant. Furthermore, few significant associations were found between negative symptoms and use of specific services (e.g., day care costs, residential costs, community services). This is in line with the study by McGurk et al. (2004), which reported that severity of symptoms, including negative symptoms, was not related to service use.

Several potential study limitations should be recognised. First, the EPSILON study was not powered for testing hypotheses on the impact of negative symptoms on costs. Thus, the lack of statistical significance in the regression models for each country may be due to low statistical power, and most emphasis should therefore be placed on the pooled analysis. Furthermore, despite the multicentre design, some centres provided little data, and the resultant high levels of variability could influence the statistical analyses. The use of a multinational design can also introduce confounders due to differences in the availability and effectiveness of care, and to differences in the sociocultural context that can influence the roles of families and the impact of a long-term illness such as schizophrenia. This may account for the apparently anomalous results in Santander, where the prevalence and severity of negative symptoms were relatively high, but the direct costs of care were generally low. Lastly, it should be noted that the BPRS scale used in the EPSILON study was not specifically designed to assess negative symptoms in patients with schizophrenia. Finally, although we have controlled for various background and clinical characteristics, there are likely to be other confounders, *e.g.*, duration of illness and pharmacotherapy (Bressan et al. 2002) that have not been included or measured. In light of these various limitations, the results presented here should be interpreted cautiously. To confirm these findings, further research could be undertaken using scales that have been validated to assess the negative symptoms of schizophrenia, employing a larger sample, prospectively following patients over time rather than examining associations in a cross-sectional design, and including data collection on all relevant clinical covariates. Ideally, it would also be good to avoid the complication of drawing data from multiple countries. In addition, it would be helpful to also use multi-level models to explore these relationships.

Our finding that negative symptoms are related to higher inpatient costs is pertinent to discussions of schizophrenia treatment and care because treating these symptoms can be so difficult. The continued impact of unresolved negative symptoms on day-to-day functioning and health care utilisation can, as we have seen, have a significant economic impact on health care systems. Improved pharmacotherapeutic and

psychological treatment for negative symptoms (*e.g.* as proposed by Horan et al. 2008) would have the potential to reduce overall resource use and the cost of schizophrenia treatment.

Acknowledgments

This work was supported by Organon, a part of Schering-Plough Corporation, and Pfizer Inc, and editorial services were provided by Karen Zimmermann at Complete Healthcare Communications, Inc. and Kelly Halton at the Institute of Psychiatry.

Appendix. *Rotated Principal-Component Matrix for Brief Psychiatric Rating Scale Items*

BPRS Item	Component 1 (positive symptoms)	Component 2 (mania)	Component 3 (depression/ anxiety)	Component 4 (negative symptoms)
1 – somatic concern			0.472	
2 – anxiety			0.710	
3 – depression			0.759	
4 – suicidality			0.631	
5 – guilt			0.414	
6 – hostility				
7 – elevated mood		0.590		
8 – grandiosity	0.458			
9 – suspiciousness	0.678			
10 – hallucinations	0.696			
11 – unusual thought content	0.814			
12 – bizarre behavior	0.444	0.469		
13 – self-neglect		0.475		
14 – disorientation	0.435			
15 – conceptual disorganization	0.641			
16 – blunted affect				0.796
17 – emotional withdrawal				0.754
18 – motor retardation				0.645
19 – tension			0.552	
20 – uncooperativeness		0.461		
21 – excitement		0.650		
22 – distractibility		0.647		
23 – motor hyperactivity		0.563		
24 – mannerisms & posturing		0.499		

BPRS=Brief Psychiatric Rating Scale.

References

American Psychiatric Association (APA) (2000). *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., Text Revision. American Psychiatric Association, Washington, DC.

Becker T, Knapp M, Knudsen HC, Schene A, Tansella M, Thornicroft G, Vazquez-Barquero, JL (1999). The EPSILON study of schizophrenia in five European countries. Design and methodology for standardising outcome measures and comparing patterns of care and service costs. *British Journal of Psychiatry* 175, 514-521.

Becker T, Knapp M, Knudsen HC, Schene AH, Tansella M, Thornicroft G, Vazquez-Barquero JL (2000). Aims, outcome measures, study sites and patient sample. EPSILON Study 1. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *British Journal of Psychiatry* 177, Suppl 39, S1-7.

Bressan RA, Costa DC, Jones HM, Ell PJ, Pilowsky LS (2002). Typical antipsychotic drugs - D(2) receptor occupancy and depressive symptoms in schizophrenia. *Schizophrenia Research* 56, 31-6.

Chisholm D, Knapp MRJ, Knudsen HC, Amaddeo F, Gaite L, van Wijngaarden B (2000). Client Socio-Demographic and Service Receipt Inventory–European Version: development of an instrument for international research. EPSILON Study 5. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *British Journal of Psychiatry* 177, Suppl 39, S28-33.

Davies LM, Drummond MF (1994). Economics and schizophrenia: the real cost. *British Journal of Psychiatry* 165, Suppl 25, S18-21.

Dixon L, Lyles A, Smith C, Hoch JS, Fahey M, Postrado L, Lucksted A, Lehman A (2001). Use and costs of ambulatory care services among Medicare enrollees with schizophrenia. *Psychiatric Services* 52, 786-792.

Dunn G, Mirandola M, Amaddeo F, Tansella M (2003). Describing, explaining or predicting mental health care costs: a guide to regression models. Methodological review. *British Journal of Psychiatry* 183, 398-404.

Endicott J, Spitzer RL, Fleiss JL, Cohen J (1976). The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry* 33, 766-771.

Evers SM, Ament AJ (1995). Costs of schizophrenia in The Netherlands. *Schizophrenia Bulletin* 21, 141-153.

Horan WP, Kern RS, Shokat-Fadai K, Sergi MJ, Wynn JK, Green MF (2008). Social cognitive skills training in schizophrenia: An initial efficacy study of stabilized outpatients. *Schizophrenia Research* Oct 16 (Epub ahead of print).

Hu TW (2006). Perspectives: an international review of the national cost estimates of mental illness, 1990-2003. *J of Mental Health Policy and Economics* 9, 3-13.

Knapp M, Chisholm D, Leese M, Amaddeo F, Tansella M, Schene A, Thornicroft G, Vazquez-Barquero JL, Knudsen HC, Becker T (2002). Comparing patterns and costs of schizophrenia care in five European countries: the EPSILON study. European Psychiatric Services: Inputs Linked to Outcome Domains and Needs. *Acta Psychiatrica Scandinavica* 105, 42-54.

Knapp M, Mangalore R, Simon J (2004). The global costs of schizophrenia. *Schizophrenia Bulletin* 30, 279-293.

Lukoff D, Neuchterlein KH, Ventura J (1986). Manual for the expanded Brief Psychiatric Rating Scale (BPRS). *Schizophrenia Bulletin* 12, 594-602.

Mangalore R, Knapp M (2007). Cost of schizophrenia in England. *Journal of Mental Health Policy and Economics* 10, 23-41.

McGurk SR, Mueser KT, Walling D, Harvey PD, Meltzer HY (2004). Cognitive functioning predicts outpatient service utilization in schizophrenia. *Mental Health Services Research* 6, 185-188.

Mohr PE, Cheng CM, Claxton K, Conley RR, Feldman JJ, Hargreaves WA, Lehman AF, Lenert LA, Mahmoud R, Marder SR, Neumann PJ (2004). The heterogeneity of schizophrenia in disease states. *Schizophrenia Research* 71, 83-95.

Oliva-Moreno J, Lopez-Bastida J, Osuna-Guerrero R, Montejo-Gonzalez AL, Duque-Gonzale, B (2006). The costs of schizophrenia in Spain. *European Journal of Health Economics* 7, 182-188.

Oliver JP, Huxley PJ, Priebe S, Kaiser W (1997). Measuring the quality of life of severely mentally ill people using the Lancashire Quality of Life Profile. *Soc Psychiatry Psychiatric Epidemiology* 32, 76-83.

Phelan M, Slade M, Thornicroft G, Dunn G, Holloway F, Wykes T, Strathdee G, Loftus L, McCrone P, Hayward P (1995). The Camberwell Assessment of Need: the validity and reliability of an instrument to assess the needs of people with severe mental illness. *British Journal of Psychiatry* 167, 589-595.

Rice DP, Miller LS (1998). Health economics and cost implications of anxiety and other mental disorders in the United States. *British Journal of Psychiatry* 173, Suppl 34, S4-9.

Ruggeri M, Dall'Agnola R (1993). The development and use of the Verona Expectations for Care Scale (VECS) and the Verona Service Satisfaction Scale (VSSS) for measuring expectations and satisfaction with community-based psychiatric services in patients, relatives and professionals. *Psychological Medicine* 23, 511-523.

Ruggeri M, Koeter M, Schene A, Bonetto C, Vazquez-Barquero JL, Becker T, Knapp M, Knudsen HC, Tansella M, Thornicroft G (2005). Factor solution of the BPRS-expanded version in schizophrenic outpatients living in five European countries. *Schizophrenia Research* 75, 107-117.

Steinert T, Krueger M, Gebhardt RP (1999). Costs of treatment and outcome measures in schizophrenia. *European Journal of Psychiatry* 13, 209-214.