Nordic region. No single study was found from Central and Eastern Europe. Hence, with the changing patterns of disease and patient management, and major gaps in geographical coverage, there is great need for more recent studies in the field with sound cost-of-illness methodology.

Conclusion

There is a fairly poor evidence base available on cost of substance abuse in Europe, where the most recent studies are performed in the middle of the 1990s, and cover only the major European countries and the Nordic region. There is little coherence in methodology across studies, which makes comparison of cost results across studies less viable. However, with the development of the cost-of-illness methodology and more resources allocated to attention and research in the area, the knowledge base will increase exponentially over time. Nevertheless, today there is a great need for further research on the burden of substance use disorders. before full health economic evaluations on treatment alternatives in the field can be performed.

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Economic evidence in affective disorders: a review

Introduction

This review is part of the set of literature reviews being produced in the project Cost of Disorders of the Brain in Europe sponsored by the European Brain Council (EBC). The objective of this review is to provide an overview of the available economic evidence in the literature on affective disorders in Europe.

Objective

The objective of this research is to review the published literature of cost and costof-illness assessments for the mood (affective) disorders in Europe. More specifically, the following disorders within the mood/affective disorders are reviewed:

- Bipolar 1 and 2
- Depression
- **D**ysthymia

Methods

A systematic literature search and review was conducted. The literature was searched using the electronic databases PubMed/ MEDLINE. The identified references were screened using a two-step approach prior to inclusion of reference in final review:

Title, keywords and abstracts for all identified references in the literature search were screened for an assessment of eligibility and inclusion in review;

Full articles that in the first screening step were identified as potentially elligible were retriefed and reviewed for a final assessment of eligibility for inclusion in review. Once identified as eligible for inclusion in the review, data were extracted for inclusion in final literature review. Additionally, the reference lists of the identified potentially eligible studies were hand-searched for identification of additional references. Only literature in English was reviewed.

Literature search strategy

The literature searches were based on combined searches using disease-specific, economic-specific and country-specific search terms. The specific terms used in the search strategy is specified in the following sections.

Disorder search terms

The following disorder-specific search terms were used in the literature searches:

- bipolar OR bipolar disorder OR manic depressive
- depression OR depressive disorder
 dysthymia
- Table 1

Economic search terms

The following economic search terms were used in the literature searches:

- Health economics OR
- Economics OR
- Costs OR Cost analysis OR
- Cost of illness OR
- Burden of illness OR
- Economic evaluation OR
- Cost effectiveness OR
- Cost utility OR
- Cost benefit OR
- Cost minimization OR Cost minimisation

Countries

The literature search included a search of all current 25 EU membership countries, as well as Norway, Switzerland and Iceland.

EU member states. Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, The Netherlands, Aus-

Literature search and screening results overview								
	Bipolar	Depression	Dysthymia					
No. of identified studies in initial literature search	19	297	1					
No. of studies eligible for inclusion in final review	3	6	0					
No. of studies by country								
France	2							
Spain		1						
Sweden		1						
UK	1	4						

tria, Portugal, Finland, Sweden, United Kingdom, Czech Republic, Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia

Other European countries. Norway, Switzerland, Iceland

Results

Literature search results

• Table 1 summarizes the findings from the initial literature search using the above specified search strategy and the number of studies identified as eligible for inclusion in the review after screening.

As seen from **Table 1**, very few studies were identified as eligible for inclusion in the review. No studies were identified for dysthymia. Only three studies for bipolar/mania (of which two in France and one in UK), and six studies in depression of which four in UK, and one in Spain and Sweden, respectively.

The following sections summarise the main findings from the detailed review of the identified bipolar/mania and depression studies.

Bipolar/mania

In the following, the main findings from the reviewed bipolar/mania studies are discussed and the detailed data extracted from the reviewed studies are presented in a set of tables. **Table 2** presents the study characteristics, **Tables 3 – 5** present costs as presented in the studies in origi-

Table 2

Bipolar/mania study characteristics

	· · · · · · · · · · · · · · · · · · ·					
Country	Reference	Approach/Design	Follow-up/ Time frame	Sample/Prevalence	Currency	Year
France (1)	[1]	Retrospective chart review to estimate direct costs following hospitalisation for manic episodes in France (incl costs for the hospitalisation!)	3 months	n=137	Euro	1999
France (2)	[2]	Top-down prevalence-based estimation of hos- pitalisations and inpatient care costs of manic episodes in France	1 year	0.82%; 390 000 patients, with 0.68 episodes per patient per year	Euro	1999
UK	[3]	Top-down prevalence-based cost-of-illness study. NHS registry and database approach to estimate cost of bipolar disorder in the UK	1 year	0.5%; ~297 000 patients	GBP	1999/ 2000

Table 3									
Total cost	per patien	t (original curren	cy/year), bipola	ar/mania	a				
Country	Referen	ce Total costs	Direct medica	l costs	Non-medical co	st Indirect	costs Cu	rrency	Year
France (1) ^a	[1]	22 296	22 296				€		1999
France (2)	[2]	3333	3333				€		1999
UK	[3]	6922	667		292	5963	GB	P	1999/2000
^a 3 months' re	sults presented	1							
Table 4									
Direct cos	t per patier	nt (original currer	ncy/year), bipo	lar/man	ia				
Country	Reference	Total direct costs	Inpatient care	Drugs	Out-patient c	are Devices	/Procedures	Currency	Year
France (1)	[1]	22 296	22 128	72	96			€	1999
France (2)	[2]	3333	3333					€	1999
UK	[3]	667	243	29	392	4		GBP	1999/2000
Table 5									
Indirect co	ost per pati	ent (original curr	ency/year), bip	olar/ma	ania				
Country	Ref	Total indirect cost	s Short term	absence	Early retire	ement M	ortality	Currency	Year
France (1)	[1]						4	€	1999
France (2)	[2]						+	€	1999
UK	[3]	5963	512		5084	30	57 (GBP	1999/2000
Table 6									
Total cost per patient (€, 2003), bipolar/mania									
Country	Refer	ence Total co	sts Total di	rect medi	ical costs	Total non-med	lical costs	Total ind	irect costs
France (1) ^a	[1]	24 092	24 092						
France (2)	[2]	3602	3602						
UK	[3]	11 205	1080			472		9653	
^a 3 months' results presented									

nal currency/year. **Table 3** presents the findings for total cost and its main cost components, direct medical and non-medical cost as well as indirect costs. **Table 4** presents the findings for total direct medical costs and its main components, inpatient care, drugs, outpatient care and devices/procedures. **Table 5** presents the findings for total indirect cost and its main components, short-term absence, early retirement and mortality, respectively.

To allow a comparison of the available data between different studies within a given country as well as between studies across countries the following **Tables 6** -8 present costs inflated and converted to cost levels expressed in ϵ , in the cost ba-

se level of year 2003. **Table 6** presents the findings for total cost and its main cost components. **Table 7** presents the findings for total direct medical costs and its main components and **Table 8** presents the findings for total indirect cost and its main components.

All costs are presented in terms of cost per patient, wherever possible. If no perpatient cost data are presented in a specific study, the presented overall cost estimates per country and cost category are used together with the available estimate of overall prevalence of the disorder to calculate the per-patient cost levels. If no prevalence details are given in a given study, a remark is made in the study overview table and only the total cost estimate per category/country is presented for these studies.

As seen from the study characteristics presented in **Table 2**, one of the two French studies, France (1): Olie and Levy [1], is based on a retrospective chart review where the direct cost for manic episodes 3 months following hospitalisation was estimated for a sample of n=137 patients. The presented cost data for this study have not been annualised, since this would provide an overestimate of the annual cost following hospitalisation.

The other study from France, France (2): de Zelicourt et al. [2], is based on prevalence-based top-down estimates of the annual cost of hospitalisation and in-

Table /								
Total dir	ect cost p	per patient (€, 200)3), bipolar/mania					
Country	Ret	ference	Total indirect costs	Short-	term absence	Early retirement	Mortality	
France (1)	[1]							
France (2)	[2]							
UK	[3]		9653	828		8230	594	
Table 8								
Indirect	cost per	patient (€, 2003),	bipolar/mania					
Country	Ret	ference	Total indirect costs	Short-	term absence	Early retirement	Mortality	
France (1)	[1]							
France (2)	[2]							
UK	[3]		9653	828		8230	594	
Table 9								
Reviewe	d depres	sion studies char	acteristics					
Country	Reference	ce Approach/Desig	ın		Follow-up/ time frame	Sample/prevalence	Currency	Year
Spain	[4]	Cross-sectional/ on untreated pa Retrospective ba prior to enrolme for sub-clinical a without comorb average across t	multinational study (LIDO tients (treated patients ex iseline assessment - 3 mo nt. Average per-patient co nd clinical depression wit idities. (Results presented he four groups!) Total dire). Focus ccluded). nths osts h and l for the cct costs	3 months	n=472 (from Spanish site in Barcelona) of which n=134 (subclinical, disc- rete), n=124 (subclinical, comorbid), n=116 (clinical, discrete), n=98 (clinical, comorbid)	ESP	2000
Sweden	[5]	Top-down preva direct costs	lence-based approach. To	otal		Estimate of prevalence (no. of pat's with depression -96) not presented!	SEK	1996
UK (1)	[6]	Top-down preva Total direct costs	lence-based cost-of-illnes in the UK	ss study.	1 year	n/aª	GBP	1990
UK (2)	[7]	Top-down preva Total costs (incl.	lence cost-of-illness study indirect costs) in the UK	/.	1 year	n/a	GBP	1990
	[8]	Top-down preva Total direct costs	lence cost-of-illness study in the UK	/.	1 year	n/a ^a	GBP	1990
UK (3)					C			n/a

patient care costs for manic episodes in France. No other costs are provided from this study. The UK study, Das Gupta and Guest [3], is a more traditional cost-of-illness study based on NHS statistics (hospital episode statistics, drug sales statistics etc.) and provides overall costs for bipolar disorder to the UK including direct medical and non-medical costs as well as estimates of indirect costs to the UK society for bipolar disorder.

Based on the cost data presented in the common currency and cost base-year (€, 2003) in **Tables 6–8** and **Figs. 1** and 2, the few studies present clearly different cost patterns. First, the cost estimates differ within France for manic episodes, and second, the cost estimates differ between France and the UK. In the study by Olie and Levy [1] the total cost estimate is \notin 24 092 (for a 3-month period), consisting only of direct costs, of which the major proportion (98.6%) is inpatient care, whereas the study by de Zelicourt et al. [2] estimates the inpatient care costs to \notin 3602. These data differ significantly between each other and

Table 10

Total cost per patient per year (original currency/year), depression										
Country	Reference	Total costs	Direct medical costs	Non-medical cost	Indirect costs	Currency	Year			
Spain	[4]	214 324	81 616		132 708	ESP	2000			
Sweden ^a	[5]	1 836 000 000	1 836 000000			SEK	1996			
UK (1) ^a	[6]	333 000 000	333 000 000			GBP	1990			
UK (2)	[7]	2337	243	39	2055	GBP	1990			
UK (3) ^a	[8]	206 600 000	206 600 000			GBP	1990			
UK (4)	[9]	18 137	17 306			USD	n/a Paper submitted 2001			

Table 11

Direct cost per patient per year (original currency/year), depression									
Country	Reference	Total direct costs	Inpatient care	Drugs	Out-patient care	Currency	Year		
Spain	[4]	81 616	29 524		52 092	ESP	2000		
Sweden ^a	[5]	1 836 000 000	599 000 000	748000000	489 000 000	SEK	1996		
UK (1) ^a	[6]	333 000 000	250 000 000	55000000	28 000 000	GBP	1990		
UK (2) ^a	[7]	243	123	33	87	GBP	1990		
UK (3) ^a	[8]	206 600 000	93 800 000	41700000	71 100 000	GBP	1990		
UK (4)	[9]	17 306	16 975		331	USD	n/a Paper submitted 2001		

also in comparison to the UK study by das Gupta and Guest [3], where the total cost estimate is € 11 205. The estimated cost in the UK study is, however estimated to be much smaller than in both of the French study estimates (€ 1080 vs. € 24 092 and € 3602). Furthermore, in the UK study the outpatient care cost accounts for 58.7% of the direct costs, whereas the corresponding estimate is 0.43% in the study by Olie and Levy [1]. The biggest part of the total costs in the UK study is the indirect costs, which are estimated to be € 9653 per patient per year, accounting for 86% of the total costs. Of these costs, early retirement accounts for around 85.3%, short-term absence 8.6% and mortality 6.1%. None of the French studies provides estimates of the indirect costs.

Both French studies are focused on estimating costs of manic episodes, whereas the UK study is focused on estimating the cost of bipolar disorder. As the manic phase of bipolar disorder is generally expected to be more demanding on healthcare resources in general, this explains the difference in cost estimates between the French and UK data.

The reason for the difference between the two French studies can be found in the differences in objective, design and studies population between the two studies. The key difference is that the France (1) study by Olie and Levy [1] is a chart review that focuses on a more severely ill population and provides an estimate of the 3 months' direct resource use and direct cost of a 3-month period following hospitalisation for a manic episode (the cost of the hospitalisation itself is included in the cost). The costs for hospitalisation accounted for 98.6% of the total direct estimated costs in this study. The other France (2) study by de Zelicourt et al. [2] is a prevalence-based topdown approach where different assumptions are combined with data from different sources to provide an estimate of the cost of manic episodes across all patients with bipolar 1 disorder in France. So the population studied in this second study is

not only the acutely ill and hospitalised, but all patients with bipolar 1 disorder. Based on this, the estimated per patient cost is naturally lower than for the hospitalised patients.

Two other important differences between the studies should be pointed out:

First, the average duration of hospitalisation for the manic episodes is estimated at 47.3 days by Olie and Levy [1], whereas the assumed duration of hospitalisation in de Zelicourt et al. [2] study is 32.4 days. A closer scrutiny reveals that the data used in de Zelicourt et al. is based on an available estimate of the inpatient stay in general psychiatric care, i.e. not bipolar/mania-specific. This difference between the studies also explains the difference in presented costs.

Second, the studies have used remarkably different unit costs for the inpatient care cost per day. The Olie and Levy [1] study use \in 21 712/47.3= \in 459, whereas de Zelicourt et al. [2] used \in 8002/32.4= \in 247. This difference also

Table 12

Indirect cost per patient per year (original currency/year), depression									
Country	Reference	Total indirect costs	Short-term absence	Currency	Year				
Spain	[4]	132 708	132 708	ESP	2000				
Sweden ^a	[5]			SEK	1996				
UK (1) ^a	[6]			GBP	1990				
UK (2)	[7]	2055	2055	GBP	1990				
UK (3) ^a	[8]			GBP	1990				
UK (4)	[9]			USD	n/a				
					Paper submitted 2001				

^a Per-patient costs not available. Specified costs are estimated total country-wide total costs

Table 13

Total cost per patient per year (€, 2003), depression									
Country	Reference	Total costs	Total direct medical costs	Total non-medical costs	Total indirect costs				
Spain	[4]	1171	446	0	725				
Sweden ^a	[5]	260 532 404	260 532 404	0	0				
UK (1) ^a	[6]	725 700 266	725 700 266	0	0				
UK (2)	[7]	5092	529	85	4478				
UK (3) ^a	[8]	450 239 264	450 239 264	0	0				
UK (4)	[9]	16 581	15 822	759	0				

^a Per-patient costs not available. Specified costs are estimated total country-wide total costs

provides an explanation for the different results presented.

Depression

In the following, the main findings from the reviewed depression studies are discussed and the detailed data extracted from the reviewed studies are presented in a set of tables. • Table 9 presents the study characteristics, • Tables 10–12 present costs as presented in the studies in original currency/year. • Table 10 presents the findings for total cost and its main cost components, direct medical and non-medical costs as well as indirect costs. • Table 11 presents the findings for total direct medical cost and its main components inpatient care, drugs, outpatient care and devices/procedures. Table 12 presents the findings for total indirect cost and its main components, short-term absence, early retirement and mortality, respectively.

The following **Tables 13–15** and **Figs 3 and 4** present costs inflated and

converted to cost levels expressed in € in 2003 year's cost level. Table 13 presents the findings for total cost and its main cost components. Table 14 presents the findings for total direct medical cost and its main components and Table 15 presents the findings for total indirect cost and its main components.

All costs are presented in terms of cost per patient, wherever possible. If no perpatient cost data are presented in a specific study, the presented overall cost estimates per country and cost category are used together with the available estimate of overall prevalence of the disorder to calculate the per-patient cost levels. If no prevalence details are given in a given study, a remark is made in the study overview table and only the total cost estimate per category/country is presented for these studies.

As seen from the depression study characteristics presented in Table 9, three of the four studies in the UK ([6], [7] and [8]) and the Swedish study [10] are top-down prevalence-based costof-illness studies that provide estimates of the overall cost of depression for the country in question using official hospital statistics and registry data. Of the four COI studies, only the UK study by Kind [7] provides estimates of the depression prevalence that can be used for calculations of the study-specific estimate of per-patient per-year costs (instead of the overall total country-level costs provided). The Spanish data come from the international LIDO study [4], which reports data from a cross-sectional retrospective assessment of resource use and costs 3 months prior to enrolment in the study for patients in Spain, Israel, Australia, Brazil, US and Russia. Finally, the 4th UK study by Creed et al. [9] is a prospective follow-up case-control study of quality-of-life and direct medical resource use/costs 5 months¹ following hospitalisation at acute med-

¹ The presented cost data are based on annualised estimates











Fig. 2 ▲ Total direct cost per patient (€, 2003), bipolar/mania



Fig. 4 ▲ Direct cost per patient per year (€, 2003), depression

ical wards in a large teaching hospital in Manchester, UK (**□** Fig. 3).

Focusing the discussion of the results on the three studies that provide estimates of per patient per year results, the results from **Table 14** and **Fig. 4** (provided in € 2003) show that the Spanish data from the LIDO study by Chisholm et al. [4] and the UK(2) study by Kind [7] provide similar estimates of the total direct costs (€ 446 in Spain and € 529 in the UK, respectively). The indirect cost estimates differ substantially between the two studies, with an estimate for Spain of € 725 and an estimate of € 4478 for the UK. Both studies include only the indirect cost due to short-term absence from work in the estimates of indirect costs, and do not provide estimates of the costs for early retirement and mortality due to depression.

The results furthermore indicate that the UK(4) by Creed et al. [9], which presents only estimates of the direct total costs, provides a substantially higher total direct costs estimate than the other UK(2) study and the Spanish study. The estimated annual direct cost for UK from this study is € 15 822, compared to the estimate of € 529 from the UK(2) study by Kind et al. This significant difference is due to the fact that the Creed et al. study is based on estimating the costs for patients during (and 5 months after) acute hospitalisation for depression/ anxiety symptoms. This is also indicated by the fact that the inpatient costs in this study account for 98.1% of the total direct costs. As a remark, it may be worth noting that the costs presented in the tables are obtained from a simple annualisation of the published 5-months costs. This may even further overestimate the costs from this study. However, the non-annualised total direct cost estimate is \notin 6592 (15 822x5/12), which is still more than ten times over the estimate in the UK(2) study.

Summary and conclusions

Based on this literature review, one obvious conclusion is that there are currently big gaps in the available literature regarding the costs of mood (affective) disorders in Europe. Very few studies reporting cost estimates for the mood (affective) disorders were found. Only three studies were found for bipolar/mania, of which two were from France and one from the UK. Only six studies were found for depression, of which four were from the UK, one from Spain and one from Sweden. In other words, there are more gaps in the available literature than findings. In particular this is true for Central and Eastern Europe (CEE),

Table 14

Direct cost per patient per year (€, 2003), depression									
Country	Reference	Total direct costs	Inpatient care	Drugs	Outpatient care	Devices/procedures			
Spain	[4]	446	161		285				
Sweden ^a	[5]	260 532 404	84 999 406	106 142 831	69 390 167				
UK (1) ^a	[6]	725 700 266	544 820 020	119 860 404	61 019 842				
UK (2)	[7]	529	267	71	190				
UK (3) ^a	[8]	450 239 264	204 416 471	90 875 979	154 946 814				
UK (4)	[9]	15 822	15 519		303				

^a Per-patient costs not available. Specified costs are estimated total country-wide total costs

Table 15

Indirect cost per patient per year (€, 2003), depression

Country	Reference	Total indirect costs	Short-term absence	Early retirement	Mortality				
Spain	[4]	725	725						
Sweden ^a	[5]								
UK (1) ^a	[6]								
UK (2)	[7]	4478	4478						
UK (3) ^a	[8]								
UK (4)	[9]								
^a Per-patient costs r	^a Per-patient costs not available. Specified costs are estimated total country-wide total costs								

where no relevant studies were found. One reason for the lack of findings from CEE could admittedly be due to the fact that the search and review has been limited to searches and reviews of studies published in the international literature in English. Additionally, this research project was focused on a search and review of available studies providing evidence of the economic cost of mood (affective) disorders. Based on this, the project search strategy did not include a systematic search of epidemiological studies which may provide data/estimates of treatment and resource use patterns such as medical visits and lost work days (without actually costing these resources).

Based on the lack of available data in this review, it is difficult, if not to say impossible, to use the identified data to extrapolate the costs in countries where no studies/data were found. Furthermore, the identified studies differ in design, which makes comparison across studies/countries difficult. One suggestion for future work in this area is to extend the search and review to a broa-

der geographical area (i.e. also include studies from the US in the review). This might not, however, give a tremendeous amount of additional findings for the mood (affective) disorders. This is apparent from two published reviews focused on the costs of mood (affective) disorders. Berto et al. [11] provide a review of the international literature of cost-ofillness studies in depression, and Kleinman et al. [12] provide a recently published review of the costs of bipolar disorder. Both these reviews take a broader geographical approach and include all available literature, which differs from the current review's focus on Europe only. In comparison to the presented findings in the current review only a handful of additional references are identified in these reviews, primarily from the United States. Another suggestion to extend the work already indicated in the discussion above is to combine the search and review results from this work with the results from the epidemiological literature review that has been done in parallel in the EBC project. The combined findings of the health economic and the epidemiological reviews should provide the most comprehensive review of the available evidence regarding mood (affective) disorders in Europe that can be used for cost predictions in countries where there are still gaps in the literature.

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Economic evidence in anxiety disorders: a review

Introduction

This review is part of the set of literature reviews being produced in the project Cost of Disorders of the Brain in Europe sponsored by the European Brain Council (EBC). The objective of this review is to provide an overview of the available economic evidence in the literature on affective disorders in Europe.

Objective

The objective of this research is to review the published literature of cost and costof-illness assessments for the anxiety disorders in Europe. More specifically, the following disease areas are reviewed:

- Panic disorders (with and without agoraphobia)
- Agoraphobia without panic disorder
- Generalised anxiety disorder (GAD)
- Obsessive compulsive disorder
- Social phobia
- Any specific phobia (animal, natural environment, blood-injection injury, situational etc.)
- Anxiety disorders [not otherwise specified (NOS)]



Fig. 1 > Total cost per patient (€, 2003), GAD and panic disorder