

Value of Generic Medicines

Health Economics Study

Study Report

for the European Generic Medicines Association

Berlin, 5 October 2015

Contact:

Dr. Martin Albrecht
T +49 30 230 809 0
martin.albrecht@iges.de

IGES Institut GmbH

Friedrichstraße 180
10117 Berlin

www.iges.de

Martin Albrecht
Xiaoyu Chen
Ariane Höer
Christoph de Millas
Richard Ochmann
Cornelia Seidlitz
Anne Zimmermann

Inhalt

1.	Study objective and approach	6
1.1	Three value dimensions of generic medicines	6
1.2	Methods	7
2.	Overall economic value of generic medicines	8
2.1	Market impact	8
2.2	Budget impact	11
2.3	Macroeconomic impact	13
3.	Patient-related value of generic medicines	14
3.1	Hypertension and antihypertensives	15
3.1.1	Market overview	15
3.1.2	Clinical evidence	15
3.1.3	Health outcomes	16
3.1.4	Treatment utilization	17
3.1.5	Effects on adherence	20
3.2	Breast cancer and adjuvant endocrine therapy	21
3.2.1	Market overview	21
3.2.2	Clinical evidence	22
3.2.3	Health outcomes	22
3.2.4	Treatment utilization	23
3.2.5	Effects on adherence	24
3.3	Depression and antidepressants	25
3.3.1	Market overview	25
3.3.2	Clinical evidence	25
3.3.3	Health outcomes	27
3.3.4	Treatment utilization	28
3.3.5	Effects on adherence	29
4.	Patient access	30
4.1	Generic market penetration	31
4.1.1	Magnitude and country variations	31
4.1.2	Differences between substance groups	34
4.2	Generic penetration, treatment utilization change, and cost-effectiveness	35
4.2.1	Hypertension and antihypertensives	36
4.2.2	Breast cancer and adjuvant endocrine therapy	37
4.2.3	Depression and antidepressants	38
5.	Conclusion	40
	Literature	43

Figures

Figure 1:	Dimensions of generic medicines' added value	7
Figure 2:	Share of generics in the pharmaceutical market in European countries, 2012	9
Figure 3:	Change of generics' market shares in European countries, 2000-2012	10
Figure 4:	Protected and Off-Patent Market Share in European countries, 2014	11
Figure 5:	Hypertension-related mortality in EU- and OECD-countries, 1980-2010	17
Figure 6:	Hypertension drugs consumption in European countries, 2000 and 2011 (or nearest year)	18
Figure 7:	Breast cancer-related mortality in selected European countries, 1995-2012	23
Figure 8:	Trends in total endocrine therapy utilization for selected countries, 2001-2012	24
Figure 9:	Development of number of suicides in selected European countries, 1980-2012	27
Figure 10:	Antidepressants consumption in European countries, 2000 and 2011 (or nearest year)	29
Figure 11:	A stylized model of generic competition	30
Figure 12:	Change of generic market share and total prescriptions of antihypertensives (Germany)	36
Figure 13:	Change of generic market share and total prescriptions of aromatase inhibitors (Germany)	37
Figure 14:	Change of generic market share and total prescriptions of SSRI (Germany)	39

Tables

Table 1:	Hypertension: drug market overview	15
Table 2:	Development of treatment and blood pressure control rates in selected European countries	19
Table 3:	Breast cancer: drug market overview	21
Table 4:	Depression: overview of relevant drugs	25
Table 5:	Generic penetration (EU average), 2000-2007	31
Table 6:	Indicators of generic competition in selected EU countries, 1998-2010	32
Table 7:	Indicators of generic competition in Germany, 2006-2014	34

1. Study objective and approach

According to the EU Commission, competition provided by generic medicines is essential to keep public budgets under control and to maintain widespread access to medicines to the benefit of consumers/patients. Generic medicines provide an opportunity to obtain similar treatments at lower costs for patients and payers, while liberating budgets for financing new innovative medicines. For these reasons, generic medicines should reach the market without unnecessary or unjustified delay. To fully benefit from the potential budget savings brought about by generic products, rapid generic uptake in volume terms and effective price competition among generic medicines producers should be facilitated. (European Commission 2009)

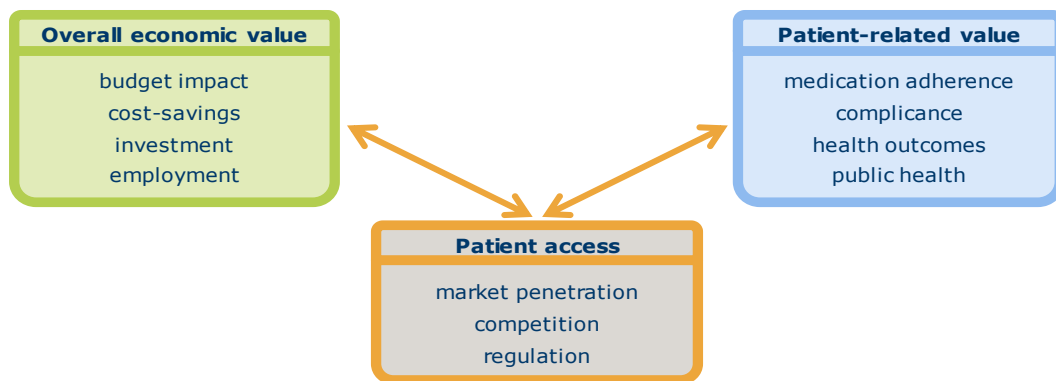
While the debate on generic medicines has been centered on affordability and cost-savings so far, their value is more comprehensive and also includes positive health impact. The European Generic medicines Association (EGA), representing the European generic and biosimilar pharmaceutical industries, has thus commissioned a health economics study to analyze the value of generic medicines more comprehensively focusing on the health-related value dimension.

1.1 Three value dimensions of generic medicines

In specific terms, the present study analyzes the added value of generic medicines based on three dimensions: their overall economic value, their patient-related value and patient access (figure 1).

- ◆ The overall economic value of generic medicines comprises budget and cost-savings plus macroeconomic parameters such as investment and employment. Thus, the first dimension covers the “traditional” perspective on generic medicines.
 - ◆ The patient-related value involves generic medicines’ health impact in terms of not only medication adherence and compliance, but also in terms of health outcomes measured by primary endpoints or by more comprehensive health (economic) benefit measures (e.g. QALY). Public health aspects, such as reduced hospitalization, will also be included. This second dimension has, to this date, been examined less and, thus, should be the focus of the projected study.
 - ◆ Patient access to generic medicines is the precondition for achieving both cost-savings and health impact. This dimension comprehends competition and market penetration as functional premises of broad and fast patient access. It also involves relevant regulative aspects (e.g. reduced co-payments).
-

Figure 1: Dimensions of generic medicines' added value



Source: IGES

1.2 Methods

The analysis is based primarily on a structured literature review in relevant literature databases with focus on medical and economic journals / references (e.g. Pubmed or Econlit). Additionally, an internet research was conducted to identify scientific reports and papers from influential stakeholders and institutions. Inclusion as well as exclusion criteria were defined and appropriate search strings developed separately for all three dimensions (overall economic value, patient-related value, and patient access).

For the research of literature considering the patient-related value as measured by clinical benefit, the focus is on relevant guidelines and recommendations which are usually based on an evidence-based literature review and thus reliably representing the current state of evidence. This structured review was conducted for three selected drug classes: antihypertensives, adjuvant endocrine therapy (breast cancer), and antidepressants. The selection criteria were prevalence, duration of therapy, and generic competition. Furthermore, the systematic review also covered studies or data on the development of health outcomes related to the selected drug groups, or indications respectively.

2. Overall economic value of generic medicines

There are three major ways in which generic medicines create economic value:

- ◆ they considerably contribute to drug supply (market impact),
- ◆ they provide substantial cost savings (budget impact),
- ◆ they contribute to macroeconomic parameters (such as employment, value added, investment) (macroeconomic impact).

2.1 Market impact

Generic medicines considerably contribute to European drug supply. In most European countries, the market share of generic medicines in volume terms exceeds 40 % (Figure 2). In Germany, the biggest pharmaceutical market in Europe¹, the volume share is much higher and has reached 73 %, on the pharmaceutical market in the United Kingdom which ranks fourth in Europe, the generic medicines' volume share was 66 %. However, the volume shares differ noticeably among the European countries: In Italy (second largest European pharmaceutical market) it was only 41 %, in France (third largest) it was 52 %.

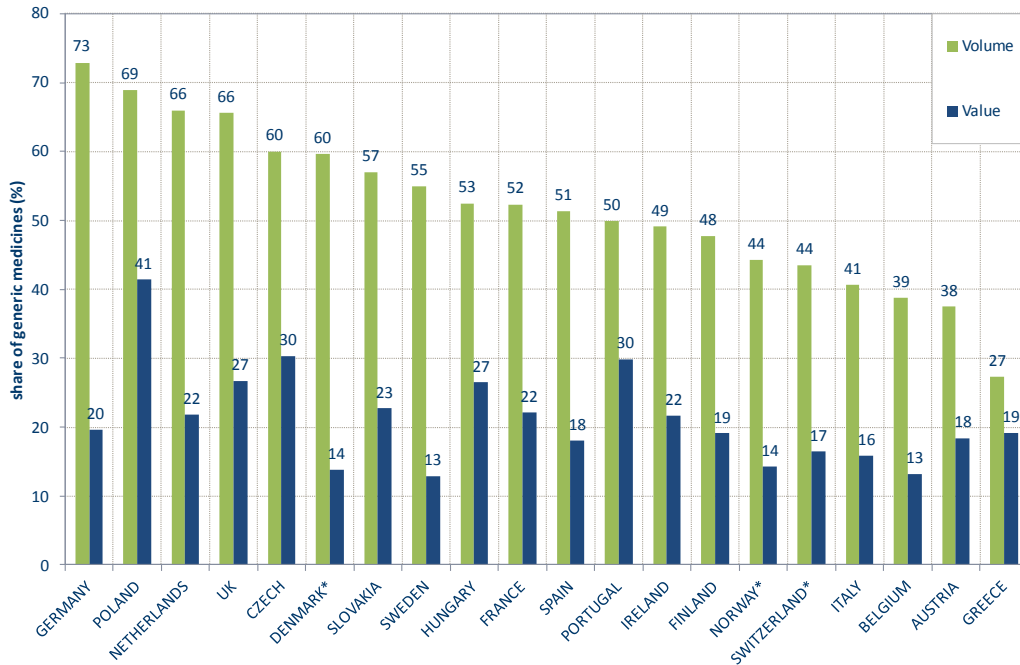
That market penetration of generic medicines in terms of volumes varies widely among the European countries is attributable to their different institutional settings and policies to promote generic substitution or INN prescribing (Busse et al. 2015, p 46 et seq.; Kanavos 2014, p 237 et seq.).

The share of generic medicines in value is in most European countries distinctly lower than in volume (except Greece). The discrepancy between volume and value share was largest in Denmark and Sweden.²

¹ The ranking of the size of pharmaceutical markets is based on total pharmaceutical sales (million US\$, purchasing power parity) according to OECD health data for the year 2012.

² Note that the discrepancy between volume and value share is actually higher in Germany as OECD data do not take into account rebates and tenders. According to IGES calculation, sales of generic medicines in 2014 amounted to 11.3 million € (based on pharmacy retail price), respectively 4.9 million € (based on manufacturer's price) being reduced by individual rebates of 3.2 million €.

Figure 2: Share of generics in the pharmaceutical market in European countries, 2014

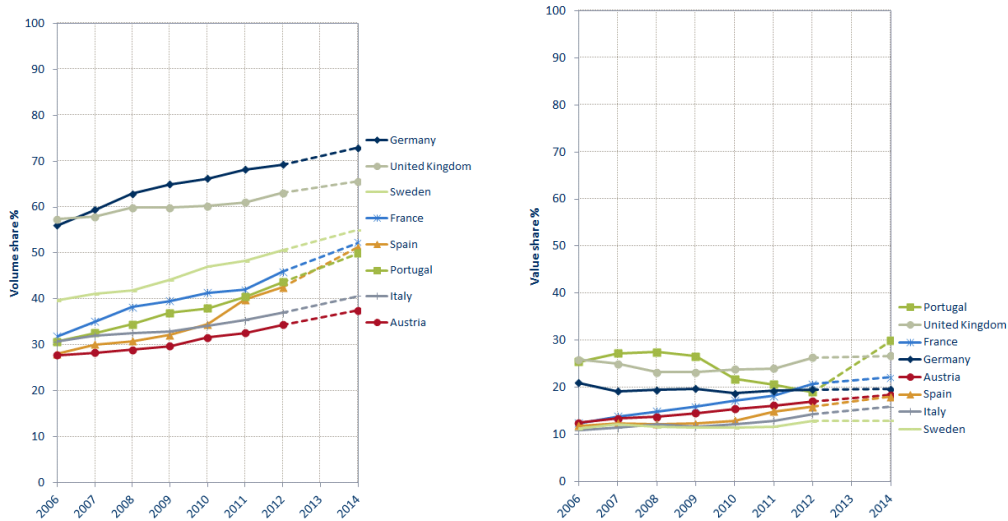


Source: IGES based on data derived from the IMS Health MIDAS database

Note: Data refer to the retail market, Rx only (prescription) and do not take into account discounts, rebates, etc.; * value data refer to 2012 (Denmark: volume data too).

The development since the year 2006 shows that – regardless of the different national levels of market penetration – the relevance of generic medicines for drug supply has been rising in the European countries, and this rise refers to volume much more than to value shares (Figure 3).

Figure 3: Change of generics' market shares in European countries, 2006-2014



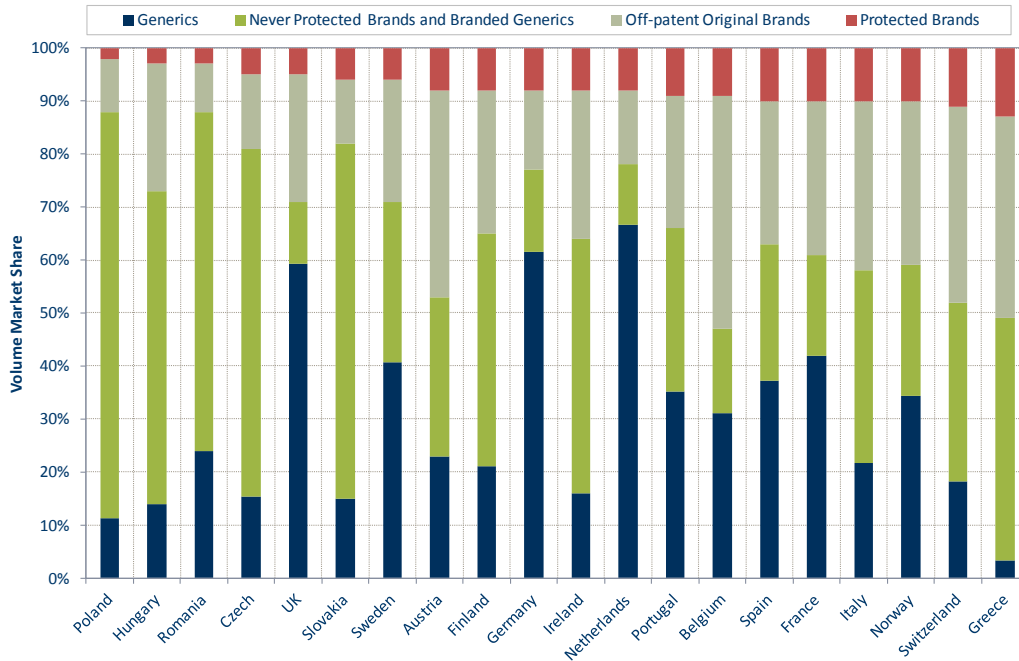
Source: IGES based on data derived from the IMS Health MIDAS database

Note: Data refer to the retail market, Rx only (prescription) and do not take into account discounts, rebates; data for 2013 not available.

A more differentiated approach to quantify the market shares of generic medicines has been developed by IMS (2015). According to this new methodology the drug market is separated into four groups: protected (on-patent) products on the one hand, and the off-patent market on the other hand, including generics, off-patent originator products, never protected brands and branded generics. In 2014, all off-patent medicines accounted for 92 % of total prescription volume (in standard units), but only 47 % of the value (as average of the European countries considered). Since 2005, the off-patent shares have increased (from 83 % of total volume and 42 % of total value) (IMS 2015, p 8).

Across the European countries, the off-patent market segments without originator products (i.e. never protected off-patent medicines and generics) had a volume share of 68 % (27 % of total value). Among the countries, these volume shares vary considerably (Figure 4). So, the market share of never protected off-patent medicines and generics was highest in the Eastern European countries Poland and Romania (88 % each), Slovakia (82 %) and Czech Republic (81 %), followed by the Netherlands (78 %) and Germany (77 %). It was lowest in Belgium (47 %) and Greece (49 %).

Figure 4: Protected and Off-Patent Market Share in European countries, 2014



Source: IGES based on IMS (2015)

Note: Non-original brands and branded generics include copy products in some countries; generics include INN branded and company branded.

2.2 Budget impact

A primary indicator to measure cost savings caused by generic market entry are price decreases for substances following patent expiry.

In its pharmaceutical sector inquiry, the European Commission found that average prices dropped by almost 20 % after the first year following the loss of exclusivity and about 25 % after two years (European Commission 2009, p 78). However, these results refer to the time period 2000-2007 and to the average of 17 Member States. The Commission also stated considerable variation between the EU Member States and across medicines. So in some cases, the average price decrease was as high as 80-90 %.

The European Commission concluded that savings through generic competition could have been higher if there were no delays of market entry. The average time to entry exceeded seven months. Had the entry been immediate, savings could have been 20 % higher, respectively, expenditure 5 % lower.

A more recent study by Kanavos (2014) for the time period 1998-2010 confirms a significant variability of price declines and their speed across European countries. Price declines ranged from 16 % (Italy) to 59 % (Sweden) one year after patent expiry, increasing from 21 % (Italy) to 70 % (Sweden) after two years.

This study also found that in some countries generic entry is considerably lower than in other countries, thus savings potential has not been fully exploited. While the “speed of genericisation” was high in the UK, Finland, Germany, France and Denmark, it was low in Greece, Sweden and Austria.

Current data for Germany show the variability of price decreases across substance groups reflecting differences in the strength of competition (Albrecht/de Millas 2014a). According to that, the higher the average market share of generic medicines in terms of volume reached after patent expiry, the stronger the prices decreased. So during the time period 2006-2014, price decreases two years after patent expiry ranged from 66 % average across substance groups where generic medicines volume share exceeded 90 % to only about 4 % average across substance groups reaching just 21 % generic market share.

While cost savings in terms of price decreases can be measured without any serious methodological difficulties, there is no generally accepted approach to calculate cost savings in terms of a precise budget impact. In fact, there is a wide range of methods how to estimate cost savings. One approach, for example, is to develop counterfactual scenarios to compare actual pharmaceutical expenditure with fictitious expenditure which might have occurred without generic market entry (see for example Dylst et al. 2015). IMS recently calculated for the EU market that spending on medicines in 2014 was 100 billion Euro less than it would have been if prices had not been lowered with the introduction of generic medicines (IMS 2015, p 9). This calculation was based on the difference between current prices of off-patent products and average prices in the last 10 years before patent expiry which is 61 % as weighted average for 14 EU markets representing 91% of total EU market in values. Some other methods, such as calculations based on international price comparisons, gives rise to controversy among health economists (see for example Cassel/Ulrich 2012). According to the EGA, generic medicines bring savings of 40 billion Euro to the EU Member States every year.³

With regard to cost savings caused by generic medicines, tender systems for outpatient pharmaceuticals should be considered as well. In recent years, tenders have become an established and preferred means of procuring primarily off-patent medicines used by sickness funds and other healthcare payors. In a former study, Kanavos has analyzed tender systems in the Netherlands and Germany (Kanavos et al. 2012). The study reports that the tender prices achieved in both countries were well below list and molecular reference prices. In the Netherlands, the discount off the price at patent expiry frequently exceeded 93 % to 95 %; for Germany, a similar range was suggested.

Consequently, the study stated that savings achieved by tendering can be significant. According to current financial statistics for the German sickness funds, gross savings caused by individual rebate contracts which are mainly based on tendering accounted for 3.2 billion Euro in 2014 (Häussler et al. 2015). About 14 % of

³ http://www.egagenerics.com/images/Website/003_EGA_FS_Generic_medicines_Web.pdf

the so-called rebate market was attributable to originator products.⁴ A minor part of the savings (about 250 million Euro) was offset by reductions of co-payments linked to rebated pharmaceuticals.

Kanavos et al. (2012) regard the competition caused by tenders rather as “race towards the bottom, as manufacturers are not aware of each other’s pricing strategy and are prepared to outbid each other by offering a price close to marginal cost in order to win the tender and stay on the market”. For the authors it “is evident that low prices at this level pose questions around sustainability over the longer term” (Kanavos et al. 2012, p 44).

2.3 Macroeconomic impact

The pharmaceutical industry is widely considered as high value-creating sector of the economy. In the 28 EU Member States, the pharmaceutical industry employed about 690,000 people in 2013 (EFPIA 2014). On average of the 28 EU Member States, wages and salaries in the pharmaceutical industry (measured by total labor costs per employee) in 2012 was 64 % higher compared to overall industry (construction and services).⁵ In Germany with Europe’s biggest pharmaceutical market, value added per employee in the pharmaceutical industry was 2.8 times as high as it was for the entire economy’s average (2012).

Available statistics provide only little information on the specific contribution of the generic medicines industry to macroeconomic performance. According to recent internal surveys by the EGA, the generic medicines industry comprises over 350 manufacturing sites in Europe and generates approximately 160,000 jobs in Europe, more than 50 % of which in manufacturing (EGA 2015). Currently, 75 % of the generic medicines consumed in Europe are produced in Europe (IMS 2015, p 17). On average, generic medicines manufacturers invest between 7.3 % and 17.5 % of their turnover in research and development (EGA 2015).

In Germany as Europe’s biggest drug market, employment in the pharmaceutical industry was almost at 110,000 in 2013. According to their association, the research-based pharmaceutical companies in Germany employed about 77,000 people. The residual amounting to about 32,500 might be an upper limit to estimate employment in the generic medicines industry as this also includes manufacturers who only produce established (original) drugs without patent protection or OTC medicines and, thus, do not necessarily rate among the generic medicines industry.

Total investment in the German pharmaceutical industry amounted to 1,300 million Euro in 2012, of which 950 million Euro came from the research-based com-

⁴ http://www.arzneimittelatlas.de/gesamtmarkt/individualrabatte/individualrabatte-nach-patentstatus/index_ger.html

⁵ Source: Eurostat database <http://ec.europa.eu/eurostat/web/labour-market/labour-costs/database>

panies, so that the generic medicines industry's share might have been about 350 million Euro.

3. Patient-related value of generic medicines

The patient-related value of generic medicines was analyzed in more detail for three selected drug classes. The selection criteria applied were

- ◆ It is a drug therapy which refers to an indication area with high prevalence (i. e. a chronic disease).
- ◆ Generic market entry and competition has been proceeding for at least some years so that there is a sufficient observation period.
- ◆ It is a long lasting therapy for which there is known evidence about the benefit of medicinal treatment.

Based on these criteria, the following drug classes were selected:

- ◆ antihypertensives,
- ◆ adjuvant endocrine therapy (breast cancer),
- ◆ antidepressants.

For these drug classes, a structured review was conducted focusing on relevant guidelines and recommendations as they are usually based on an evidence-based literature review and thus reliably representing the current state of evidence. The review also includes existing evidence to which extent the relevant drug therapy is utilized in every day health care. Finally, it covered the development of health outcomes related to the selected drug groups, or indications respectively. The structured literature search was conducted in relevant databases (e. g. Pubmed) and national / European statistics.

For each drug class, the analysis results are presented as follows:

- ◆ brief overview of the drug market, listing the relevant drug classes, the active substances, and the respective starting year of generic competition;
- ◆ clinical evidence of the treatment with these substances;
- ◆ development of health outcome indicators related to the respective indication area;
- ◆ level or development of treatment utilization,
- ◆ effects on adherence / compliance.

Finally, the results are summarized with the focus on the role of generic medicines in the development of health outcomes and the utilization of pharmacotherapy.

3.1 Hypertension and antihypertensives

3.1.1 Market overview

For the treatment of hypertension, the most important drug classes for pharmacotherapy with generic competition at least for some years are diuretics, calcium antagonists, beta blocker, ACE-inhibitors, AT-II-antagonists (Table 1).

Table 1: Hypertension: drug market overview

Antihypertensive drug classes	Active substance	Generic competition (Germany / EU)
Diuretics	Furosemid HCT	1970 unknown; at least 1970s
Calcium Antagonists	Nifedepin Amlodipine	1985 2004
Beta Blocker	Bisoprolol Metropolol	1990 1996
ACE-Inhibitors	Ramipril Ramipril HCT	2003 2006
AT-II-Antagonists	Losartan	2010

Source: IGES

There has been generic competition in all drug classes, starting in the early 1970s (diuretics) up to a more recent generic market entry in the case of AT-II-antagonists (Losartan) in 2010.

3.1.2 Clinical evidence

Meta-analyses show that antihypertensives significantly and similarly reduce cardiovascular and all-cause mortality in patients with systolic and diastolic hypertension. Therapeutic recommendations in the guidelines by the European Society of Hypertension and the European Society of Cardiology are based on these results of clinical studies (ESH & ESC 2003).

Lowering blood pressure (mainly with diuretics and beta -blockers) reduces the risks of stroke (by 38 %) and coronary heart disease (CHD) (by 16 %) as shown by meta-analyses of early trials (Collins et al. 1994).

ACE inhibitors reduce the relative risk of total major cardiovascular events – a composite end point of coronary heart disease, stroke, heart failure or cardiovascular death – by 22 %, Calcium antagonists by 18 % and angiotensin receptor blockers by 10 %. These clinical effects have been quantified based on placebo-controlled trials or control regimens (Turnbull et al. 2003).

The guideline by the European Society of Hypertension and the European Society of Cardiology states that the drug treatment with the angiotensin receptor antagonists losartan and irbesartan in patients with diabetes type 2 and nephropathy is renoprotective (Guideline 2003_ESH_ESC).

With regard to the therapeutic value of generic medicines, the guideline states that the main benefits of antihypertensive treatment are due to lowering of blood pressure per se and are largely independent of the drugs employed (Guideline 2013_ESH_ESC). Furthermore, focusing on cardiovascular drugs it has been shown that there are no measurable differences between the original branded drug and its generic equivalent in terms of clinical efficacy and safety endpoints (Kesselheim et al. 2008).

To sum up, there is comprehensive evidence for the clinical benefit of antihypertensive therapies, i. e. a large number of RCTs-based evidence. Additionally, it has been shown that there are neither clinically relevant differences between drug classes nor between original branded drugs and its generic equivalents.

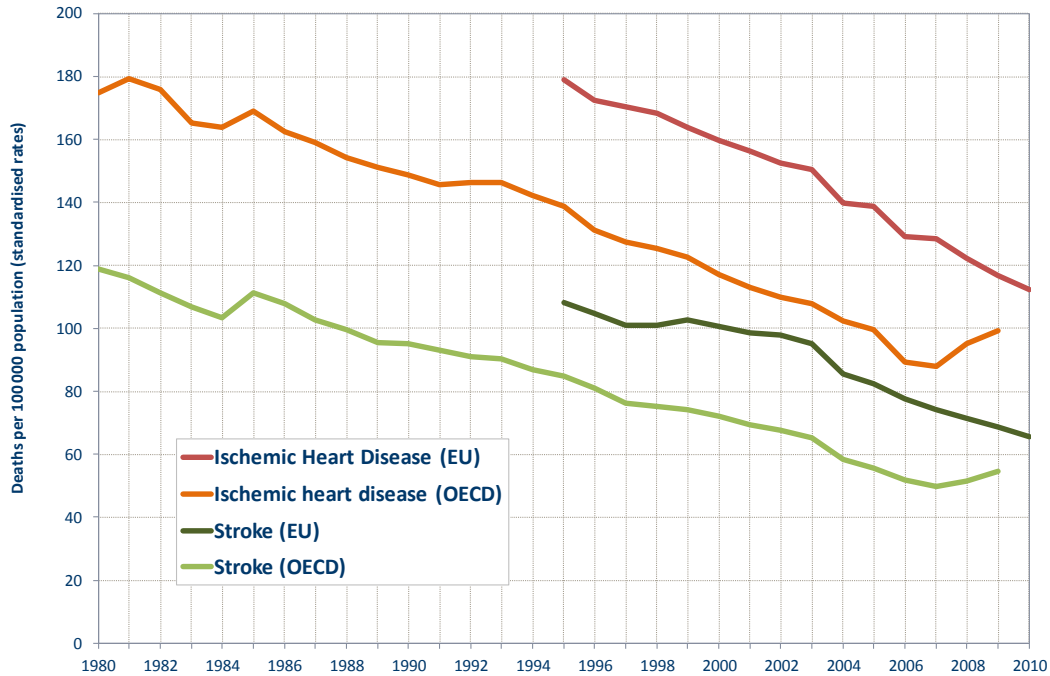
3.1.3 Health outcomes

The next step is to look at how the clinically evident benefits of hypertension treatment by medicines are transferred into population-related health. There are two well observed health outcome indicators which can be used for that purpose since they directly relate to the major clinical study endpoints for hypertension: mortality caused by stroke and mortality caused by ischemic heart disease.

According to OECD and Eurostat health statistics, both stroke mortality and mortality caused by ischemic heart disease decreased in the EU countries since 1980 (Figure 5).⁶ One of the designated causes are better medicinal treatment options, however, the observed development has to be explained multifactorially as there are other causes identified such as smoking reduction, better hypertension control, and the implementation of guidelines.

⁶ Exceptions are Hungary and Poland, where mortality rates have increased. The differences between the EU and OECD mortality levels may partially be attributed to different age-standardizations.

Figure 5: Hypertension-related mortality in EU- and OECD-countries, 1980-2010



Source: IGES based on OECD health statistics

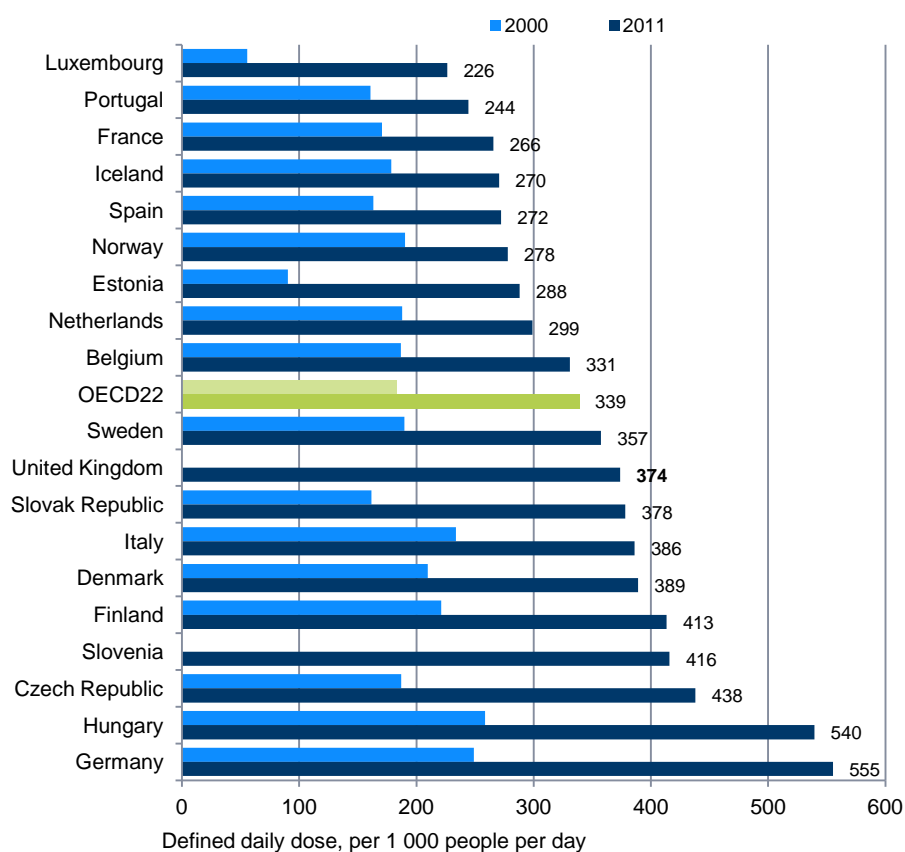
In Germany, stroke mortality decreased between 1998 and 2010 by about 50 % while the prevalence of hypertension has been stable (about one third of the population between 18-79 years) (RKI 2015).

3.1.4 Treatment utilization

With regard to the particular contribution of pharmacotherapy, improvements in health outcomes such as mortality should be reflected in similar trends of treatment rates.

OECD data shows that utilization of hypertension drugs has increased considerably over the last decade (Figure 6). While in some of the large European countries (Germany, Italy, UK), the hypertension drugs consumption rate (DDD per 1,000 people per day) has been well above the OECD average, it has been below in Spain and France. In Germany, the increase of the consumption rate between 2000 and 2011 (+123 %) was also much stronger compared to the OECD average (+85 %).

Figure 6: Hypertension drugs consumption in European countries, 2000 and 2011 (or nearest year)



Source: OECD Health Statistics 2013

Note: Italy, Netherlands: 2001; France: 2009; data refers to the sum of five ATC2 categories (Antihypertensives, Diuretics, Beta-blocking agents, Calcium channel blockers and Agents acting on the Renin-Angiotensin system)

For some European countries, data on treatment rates among affected patients (and/or on blood pressure control rates) is available and shows distinct increases (Table 2).

Table 2: Development of treatment and blood pressure control rates in selected European countries

	Germany		UK		Sweden		Spain	
	1998	2011	2003	2012	1990	2010	2000/ 2001	2008/ 2010
Prevalence	ca. 33%	ca. 33%	31%	30%	38% 44% ¹	28% 36% ¹	69%	66%
Treatment rates (among affected patients)	55%	72%	42%	53%	12% ²	19% ²		
BP control rate (<140/90mmHg) (among treated patients)	42%	72%	45%	62%	30%	65%	30%	43%
Source	German Health Surveys, RKI 2015		Health Survey for England, Knott and Mindell 2002		Västerbotton County Intervention Program, NG et al. 2012		Health Survey for Spain, Banegas et al. 2015	

Source: IGES based on sources indicated

Note: 1. female /male 2. based on affected and non-affected patients

So in Germany, for example, the proportion of adults with hypertension receiving a treatment rose from 55 % (1998) to 72 % (2008-11). During the same time period, the proportion of patients with controlled blood pressure among treated patients (< 140/90 mmHg) increased from 42 % (1998) to 72 % (2008-11) (RKI 2015).

Increases of at least one of the two indicators are also reported for the UK, Sweden and Spain. Similar results were observed in Switzerland (Estoppey 2011) and the Czech Republic (Cifkova 2010).

The specific contribution of generic medicines with regard to increasing treatment rates, and thus improving health outcomes, depends on their market penetration. This has been examined in more detail under the heading “patient access” (see chapter 4).

3.1.5 Effects on adherence

Generic medicines will create a patient-related benefit if they contribute to an increased patient adherence to long-term therapy, or compliance⁷ respectively, since a lower adherence is associated with poorer health outcomes and more comorbidities (see for example Eaddy et al. 2012, Briesacher 2007). Moreover, non-adherence has an economic impact. According to a recent study (Mennini et al. 2015), an increase of adherence to anti-hypertensive therapy up to 70 % in five European countries with different baseline values⁸ would save a total of 332 million Euro, thus reducing direct cost associated with hypertension by 0.65 %. The number of cardiovascular disease events would shrink by 82,235, or almost 1 % respectively. Despite the benefits of an improved adherence, the average medication compliance rates in developed countries are estimated to be just over 50 % (Roebuck et al. 2011). The main factor causing a positive interrelation between patient adherence and generic medicines is cost sharing for drugs. Co-payments for patients generally tend to impair patient adherence to long-term therapy. As generic medicines are associated with lower prices and co-payments for patients, they counteract this adverse effect. So a positive effect of generics on adherence is expected to be more significant in health systems with relatively high patient co-payments for drugs (Eaddy et al. 2012).

Correspondingly, a positive impact of generic medicines on patient adherence can rather be found for the US health system where co-payments are, on average, higher. A recent study showed that generic medicines prescribing was associated with improved medication adherence but not in all study conditions. Particularly for the treatment of hypertension, generic medicines were associated with lower adherence unless there was no co-payment at all. Without any co-payment, adherence improved across all study conditions, regardless of the use of generic or brand medicines (Briesacher et al. 2009).

With regard to European countries, a positive impact on adherence has been shown for Italy where patients have to make co-payments for branded drugs. According to recent studies, patients receiving a generic version of amlodipine showed a significantly better persistence and compliance compared to patients with the branded drug. Patients with generic drug treatment did not experience a different risk of discontinuation compared to those starting on brand-name agents. (Colombo et al. 2013 and Corrao et al. 2014)

As in European health systems, patient co-payments for drug therapies often play a less important role than in other countries, alternative determinants of a po-

⁷ Compliance can be defined as following the physician's instructions or recommendations, whereas adherence describes the extent to which a person's behavior – taking medication, following a diet, and/or executing life-style changes - corresponds with agreed recommendations from a health care provider (WHO Adherence to Long-Term Therapy: Evidence for Action 2003).

⁸ Italy: 41,50 %, Germany: 66,90 %, Spain: 39,40 %, France: 39,00 %, England: 56,85 %.

tential positive impact of generic medicines on patient adherence have been examined. In a Dutch study, for example, substituted patients (from antihypertensive brand to generic medicine) were less likely to be non-adherent compared with non-substituted patients: Adherence after substitution was higher for substituted patients (92.4 %) vs. non-substituted patients (90.4%) although both generic and original medicines are fully covered in the Netherlands (van Wijk et al. 2006). Besides, the risk of cardiovascular hospitalization did not increase for substituted patients. An explanation may be that pharmacies usually educate patients about the reasons for generic substitution, possibly increasing awareness about the benefits of adherent drug use.

There are, however, opposing effects. A recent literature review suggests that although generic substitution is well accepted by a majority of patients, about one-third of them report negative experiences which may lead to poor adherence and medication errors (Hakonsen 2012). Patients' acceptance of generic substitution is influenced by age, educational levels, perceptions of disease, generic drug information, and depends on who informed them about the change.

To sum up, drug therapy adherence of patients is strongly influenced by the reimbursement situation with regard to generic and originator medicines and can, thus, differ significantly between countries. High(er) co-payments for branded drugs, but also education measures for patients referring to generic substitution support a positive impact of generic medicines on patient adherence. Yet, without extra attention, particularly towards elder patients, during the process of substitution, generic medicines might also negatively influence patient adherence.

3.2 Breast cancer and adjuvant endocrine therapy

3.2.1 Market overview

The analysis refers to hormone receptor-positive breast cancer which includes about two thirds of all breast cancer cases. For this indication, there are two main types of therapies: SERM and AI.

Table 3: Breast cancer: drug market overview

Adjuvant endocrine therapy drug classes	Active substance	Generic competition (Germany / EU)
Selective Estrogen Receptor Modulators (SERM)	Tamoxifen	since 1985
Aromatase Inhibitors (AI)	Anastrozole Letrozole Exemestane	since 2011

Source: IGES

While the SERM have a long-lasting experience with generic competition, for the AI generic market entry has been more recent.

3.2.2 Clinical evidence

Meta-analyses of trials of five years therapy of adjuvant tamoxifen, conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), show that breast cancer mortality was reduced by a third during the first 15 years after the start of treatment compared to no adjuvant endocrine therapy (EBCTCG 2005/2011). The recurrence rate dropped by 39 % over the time period of 15 years compared to no adjuvant endocrine therapy (EBCTCG 2011).

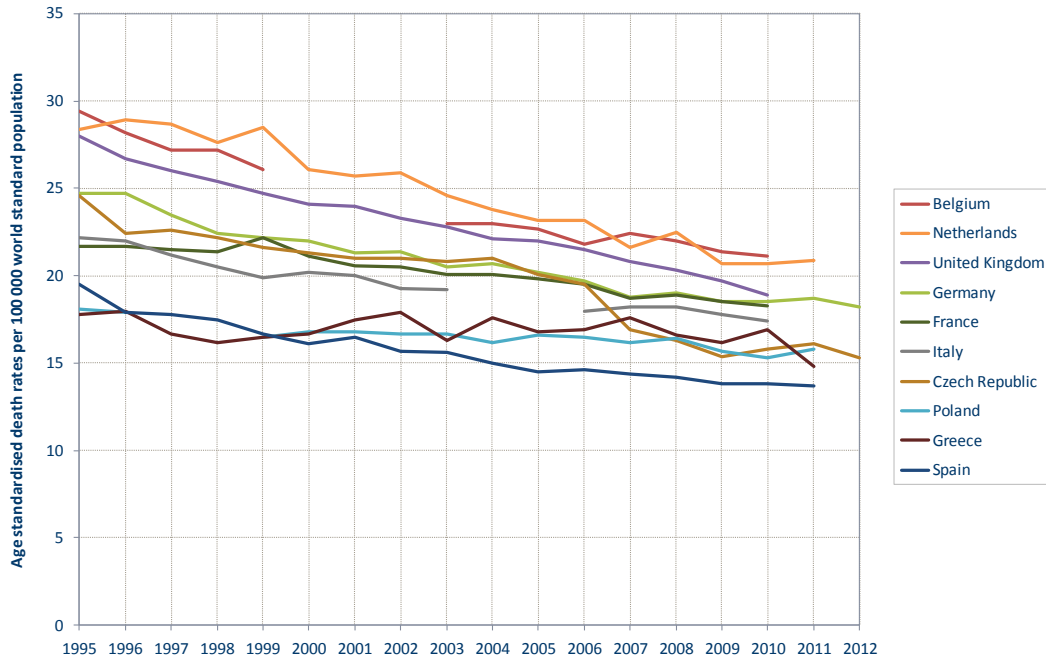
According to the Clinical Practice Guidelines by the European Society for Medical Oncology and the American Society of Clinical Oncology, in postmenopausal women aromatase inhibitors (AI) are superior in terms of disease free survival (DFS) compared to Tamoxifen. AI and Tamoxifen are equivalent in terms of overall survival. The patient's menopausal status primarily determines the choice of medication. (ESMO 2013, Burstein et al. 2010)

3.2.3 Health outcomes

In most European countries, breast cancer mortality has decreased since the late 1980s; however, the decrease varied significantly between the European countries (Autier et al. 2010).

According to WHO data covering the time period from 1995 until 2010, age standardised death rates per 100 000 of population caused by malignant neoplasm of female breast decreased in all 22 European countries for which data was available. The decrease was strongest in the Czech Republic (-35.8 %), Austria (-33.1 %), Denmark (-32.8 %) and the UK (-32.5 %). The death rate level was lowest in Spain (13.8). Figure 7 shows the development for the most populous European countries for which WHO data was available.

Figure 7: Breast cancer-related mortality in selected European countries, 1995-2012



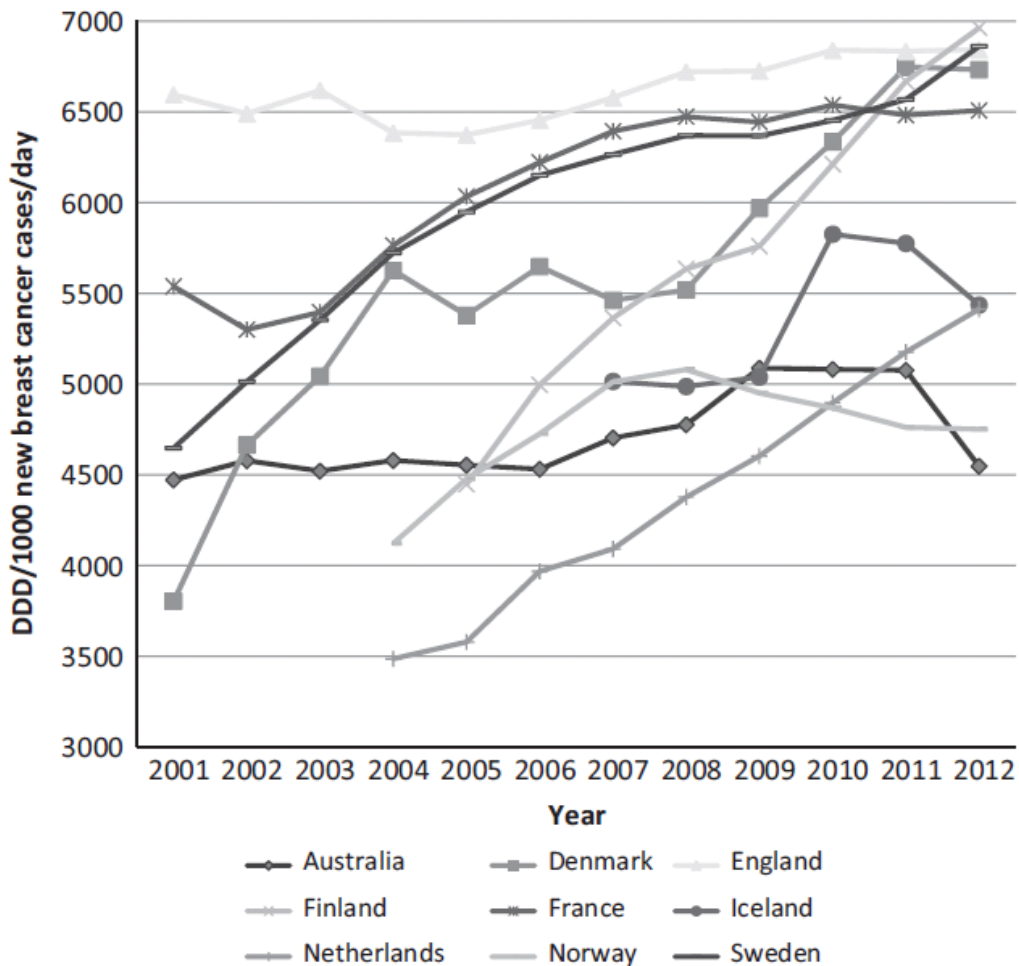
Source: IGES based on WHO healthinfo

Besides improved treatment options, early detection programs since the 1990s, e.g. mammography screening, have contributed to the reduction of breast cancer-related mortality.

3.2.4 Treatment utilization

According to a recent study, the utilization of endocrine therapies increased or remained steady over the period 2001-2012 (Kelly et al. 2014, Figure 8). Total usage was highest in France and England, and among the European countries lowest in Norway.

Figure 8: Trends in total endocrine therapy utilization for selected countries, 2001-2012



Source: Kelly et al. 2015

Note: data adjusted for breast cancer incidence and female population

The study concludes that differences in utilization observed could be due to differences in breast cancer incidence and screening programmes, prescribing behaviours, and timing of drug marketing approval and reimbursement between countries.

3.2.5 Effects on adherence

Hershman et al. 2014 investigated the change in adherence after the introduction of generic aromatase inhibitors (AI) for patients in the USA in 2010, and showed that adherence (medication possession ratio $\geq 80\%$) was positively associated with generic AI use (odds ratio = 1.53, 95% CI = 1.22 to 1.91) compared with brand-name AI and inversely associated with increased monthly co-payment. In

addition, adherence was associated with a high annual income of more than \$100k/year (odds ratio = 1.58, 95% CI = 1.17 to 2.11).

3.3 Depression and antidepressants

3.3.1 Market overview

For the treatment of depression, the most important drug classes for pharmacotherapy with generic competition at least for some years are NSMRI, others as cyclic antidepressants, SSRI, monoamine oxidase (A) inhibitors, and SNRI/NaRI (Table 4).

Table 4: Depression: overview of relevant drugs

Antidepressants drug classes	Active substance	Generic competition (Germany / EU)
Herbal antidepressant	St. John's Wort	n.a.
Non-selective monoamine reuptake inhibitors (NSMRI)	Amitriptylin Maprotilin	at least since 1986 1989
Other antidepressants	Mianserin Trazodone	at least since 1991 at least since 2003
Selective serotonin reuptake inhibitors (SSRI)	Fluoxetine Fluvoxamine	1996 1998
NorAdrenalin-reuptake-inhibitors (SNRI/NaRI)	Venlafaxin	2008

Source: IGES

While the NSMRI have a long-lasting experience with generic competition, for the SNRI generic market entry has been not until 2008.

3.3.2 Clinical evidence

According to the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders (2013),

- ◆ the ultimate goal of the *acute* treatment phase is remission;
- ◆ the goal of *continuation* treatment is to prevent a relapse, to eliminate any residual symptoms, and to restore the patient's prior level of psycho-social and occupational functioning;
- ◆ *prophylactic* treatment is aimed at preventing a new episode of depression and suicide.

In contrast to other pharmaceuticals for indications such as diabetes or hypertension, the clinical evidence for antidepressant drugs is heterogeneous.

Many new antidepressants have been introduced and approximately 35 different antidepressants in a number of classes are currently available worldwide (NCCMH 2010). The clinical effectiveness is studied in randomized clinical trials (RCT), where primary efficacy is usually placebo-controlled. In some studies, the differences in efficacy compared to placebo are small. So the placebo verum difference was estimated to be roughly between 10 % and 20 % (Storosum et al. 2001; Barbui et al. 2008; Melander et al. 2008; Leucht et al. 2012 according to WFSBP 2013). Most of the RCT studies investigated the outcome “response to treatment” after 6 or 8 weeks and it was not looked for remission (long time effectiveness).

Despite evidence from RCT is limited, there are few alternatives to using these data because better ways of assessing efficacy have not yet been developed (NCCMH 2010). Clinical studies investigating the clinical efficacy of antidepressants primarily focus on reducing the symptoms of depression (i.e. a reduction in depression rating scale scores). Some studies also cover additional outcomes i.e. cognitive abilities, quality of life etc. So it was shown, for example, that compared to supportive care alone, SSRI plus supportive care was associated with lower HDRS (Hamilton rating scale for depression) scores and higher scores on quality of life and satisfaction in depressed patients in general practice (Kendrick et al. 2009 according to WFSBP 2013).

Systematic reviews using meta-analysis suggest that antidepressant drugs, when considered individually or by class, are more effective than placebo in the treatment of major depression, whereas in patients with mild depressive episodes, antidepressants have often proved not to be more effective than placebo. Beyond that, the different substances are generally equally effective. This applies to “older” as well to “newer” classes of antidepressants. The classes of antidepressants currently available differ little in their antidepressant efficacy, all producing treatment responses of 50 % – 75 %.

There are, in contrast, significant differences in toxicity and side effects between the different classes of antidepressants. So, SSRIs are considerably safer in overdose than TCAs, generally better tolerated than antidepressants from other classes and most are available as generic preparations (NCCMH 2010).

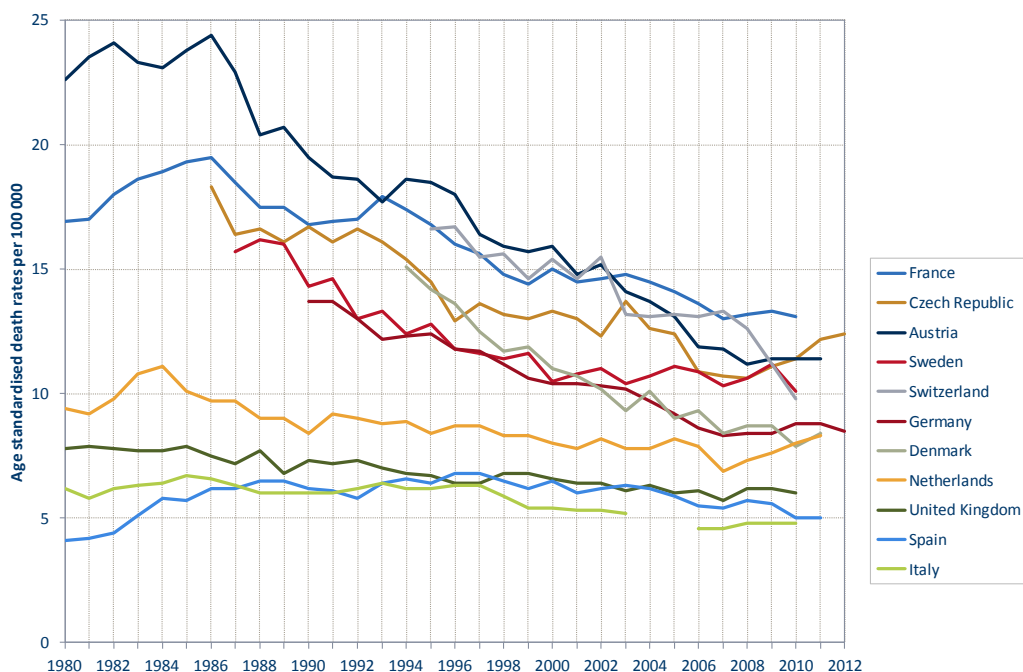
Finally, some studies have examined the effect of antidepressants particularly on suicide. There is no specific, fast acting “anti-suicidal” medication. Adding benzodiazepines to the treatment regimen may improve short-term control over suicidal acts (Furukawa et al. 2001 according to WFSBP 2013). Lithium has been shown to be effective in preventing suicide attempts and completed suicide when administered prophylactically, whether it has additional acute anti-suicidal effects is currently not known.

3.3.3 Health outcomes

As opposed to hypertensive diseases or breast cancer, depression has not yet gained major attention as a cause of death. Yet, mental illness increases the risk of developing a physical one. In Germany, for example, psychiatric and behavioural disorders had a share of 4 % of all causes of death in 2013, however, the number of cases has increased tremendously by an annual average of almost 25 % since 2001.

Besides, mental illness raises the risk of suicide. According to general estimation, the largest share of suicides (90 %) is attributable to psychiatric disorder – about more than half of those to depression. WHO data show that the age standardised death rates caused by suicide have decreased significantly in many European countries (Figure 9). So, for example, the suicide rate shrank by almost 50 % since 1980 in Austria. The decrease in Germany was about the same size, as national data shows (however, since 2007, the number has again risen slightly).

Figure 9: Development of number of suicides in selected European countries, 1980-2012



Source: IGES based on WHO Mortality Database
 Note: Intentional self-harm, all ages - both sexes

As has been pointed out, better drug supply may only explain parts of this development as not all of the suicides are caused by depression, and clinical evidence of the effect of antidepressants on suicide is fragmentary. However, epidemiological studies revealed a reduction of the frequency of suicides and increased

prescriptions of antidepressants within the last decades (Sartorius et al. 2007), but there is also a debate on whether antidepressants potentially increase the risk of suicidal behaviour (WFSBP 2013).

In a recent study by Isacson (2010), data on the toxicological detection of antidepressants in 18,922 suicides in Sweden between 1992 and 2003 were linked to registers of psychiatric hospitalization as well as registers with sociodemographic data. In the absence of other explanations, in particular explanations supported by empirical evidence, this study adds to the evidence that the decrease in suicide being demonstrated worldwide is caused by the increasing use of antidepressants.

Another relevant health outcome of antidepressant treatment is work disability, or return to work respectively. Mental illness, and particularly depression, cause strong increases of (long-term) work disability. However, evidence on the extent to which antidepressant treatment has contributed to prevent or, at least, to moderate work disability is missing.

3.3.4 Treatment utilization

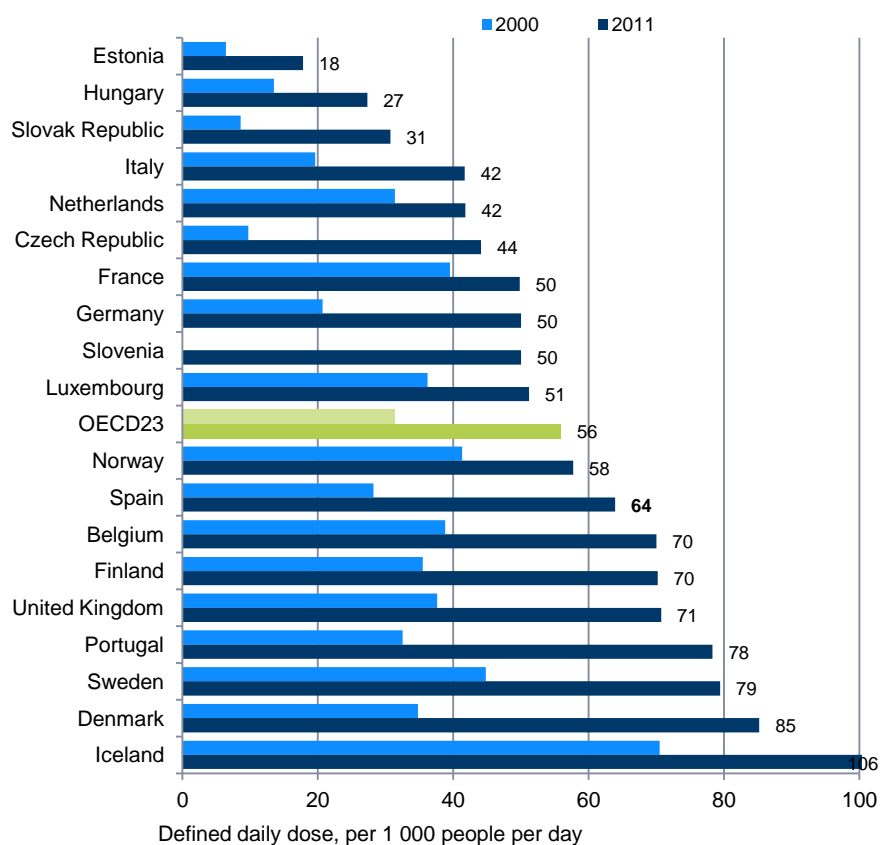
OECD data shows that utilization of antidepressants treatment has increased considerably over the last decade (The persisting differences in the consumption level among the European countries may be traced back to distinct national variations with regard to guidelines for the pharmaceutical treatment of depression and to prescribing behaviors among general practitioners and psychiatrists.

Figure 10). While in some of the large European countries (UK, Spain), the antidepressant consumption rate (DDD per 1,000 people per day) has been well above the OECD average, it has been below in Italy, France, and Germany. However, the consumption increase between 2000 and 2011 was much stronger in Germany (+142 %) and Italy (+113 %) compared to the OECD average (+79 %).

According to the OECD, greater intensity and duration of treatments are some of the factors explaining the general increase in antidepressant consumption across countries (OECD 2013). Besides, the set of indications of some antidepressants has been extended to milder forms of depression. Finally, the treatment of depression has become socially more acceptable ("burn out"-syndrome) and the willingness to seek treatment has increased.

The persisting differences in the consumption level among the European countries may be traced back to distinct national variations with regard to guidelines for the pharmaceutical treatment of depression and to prescribing behaviors among general practitioners and psychiatrists.

Figure 10: Antidepressants consumption in European countries, 2000 and 2011 (or nearest year)



Source: OECD Health Statistics 2013

Note: Italy, Netherlands: 2001; Luxembourg: 2003; France: 2009

3.3.5 Effects on adherence

With regard to antidepressants, a positive effect of generic medicines on patient adherence has been shown for the U.S. where co-payments which have been identified as a main factor for this interrelation are relatively high. Correspondingly, generic initiation of antidepressant treatment was associated with improved adherence and with a lower hazard rate of treatment disruption, and the effect was even stronger for low-income people (Bao et al. 2013). A preceding study for the U.S. found out, that discontinuation rates among patients using brand versus generic SSRI or SNRI antidepressant therapy did not differ significantly (Vlahiotis et al. 2011). Based on the lower health care costs involved, the study suggested the use of generic antidepressants as first-line agents in the treatment of major depressive disorder.

Referring to Europe, a population-based questionnaire and register study in Denmark used a prescription database to analyze associations between generic switching and non-persistence in antidepressant treatment (Rathe et al. 2015). It

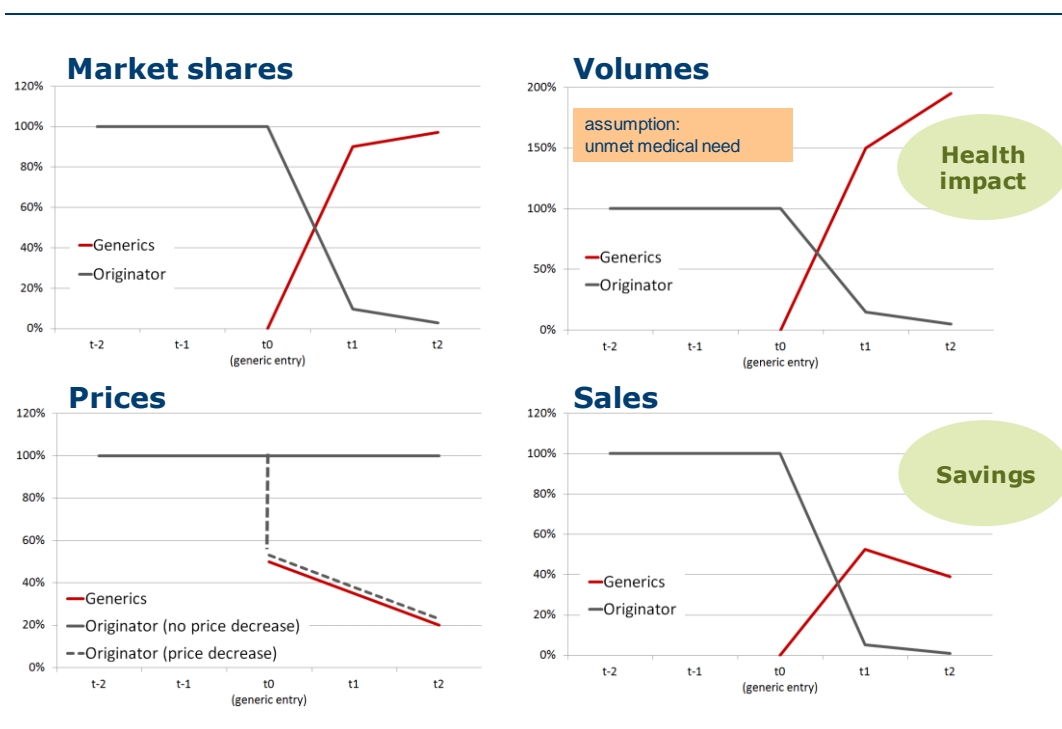
shows that patients who are first-time switchers of a specific antidepressant were at higher risk of non-persistence compared to never switchers and those having experienced previous generic switching.

In Germany, patient compliance has been discussed in the context of tendering and individual rebate contracts between sickness funds and (mainly) generic medicine suppliers. A study found significant deviations with regard to compliance with antidepressant treatment between patients who were switched to a product subject to rebate and those who were not (IMS 2010). According to the study results, the share of patients with discontinuation of antidepressant therapy within three months after switching was 22 % higher than the respective share of patients without switching. Moreover, patients with switching of antidepressants were associated with higher costs caused by increased hospitalization. The sickness funds, in contrast, argue that rebate contracts which are made exclusively with one supplier improve patient compliance since switching – otherwise caused by aut idem regulation – is ruled out for the entire contract period of two years (WIdO 2011).

4. Patient access

Patient access to generic medicines is the precondition for achieving both cost-savings and health impact. This dimension comprehends competition and market penetration as functional premises of broad and fast patient access. It also involves relevant regulatory policies.

Figure 11: A stylized model of generic competition



Source: IGES

The interaction between the economic and the patient-related value dimension of generic medicines can be depicted in a stylized model of generic competition (Figure 11) which is characterized by

- ◆ an almost complete shift in market shares between the original drug and its generic competitors,
- ◆ a sharp price decrease,
- ◆ a rise of total consumption of the substance group,
- ◆ a decrease in sales / revenues.

If there is unmet medical need, the volume increase should have a positive health impact. At the same time, price decreases lead to savings. As a result, more patients can be treated at lower cost.

In the following sections, the existing empirical evidence on patient access to generic medicines is examined, focusing on market penetration of generic medicines and the functioning of generic competition (measured by, for example, change of market shares and prices). Subsequently, generic market penetration and change in treatment utilization is looked at simultaneously for the selected drug classes.

4.1 Generic market penetration

4.1.1 Magnitude and country variations

According to the pharmaceutical sector inquiry by the European Commission, generic shares of market volume reached 30 % after one year, and 45 % after two years respectively (Table 5). Generic market shares in value terms were lower (25 % after one year, 38 % after two years).

Table 5: Generic penetration (EU average), 2000-2007

time after first generic entry	volumes	value
1 year	30 %	25 %
2 years	45 %	38 %

Source: European Commission 2009, p 87

Note: average referring to 75 top-selling molecules with loss of exclusivity 2006 (2005 respectively) or earlier

In a recent study (Kanavos 2014), basic indicators of generic competition have been analyzed for 12 European countries which are divided up between three tiers based on the perceived strength of their generic policies. The UK, Denmark, Germany, and the Netherlands form the first group characterized by high levels of generic prescribing and substitution as well as competitive pricing of (generic) pharmaceutical products. Generic market penetration in terms of volume market

share was relatively strong in these countries (Table 6): The increase was highest in the Netherlands (62.1 % two years after patent expiry), followed by Denmark (55.7 %) and Germany (54.9 %). However, generic penetration varies considerably among the study countries, reaching only 9.1 % volume market share in Greece and 15.3 % in Spain at the other extreme. Though it must be noted that there have been some considerable changes on the markets since the end of the study period 2010.

Table 6: Indicators of generic competition in selected EU countries, 1998-2010

	Ø volume market share		Ø price development ¹⁾		Ø number of generic competitors (maximum)	
	<i>months post-patent expiry</i>					
	12	24	12	24	12	24
United Kingdom	35.8 %	46.5 %	60.6	34.9	2.0 (6)	2.4 (7)
Denmark	35.9 %	55.7 %	42.9	31.2	3.5 (11)	3.8 (12)
Germany	39.0 %	54.9 %	61.8	56.1	10.8 (32)	13.6 (40)
Netherlands	38.9 %	62.1 %	61.7	58.5	1.9 (14)	4.7 (20)
Finland	23.1 %	38.4 %	50.5	36.9	3.4 (12)	4.8 (10)
Austria	12.8 %	26.9 %	61.5	59.9	2.8 (9)	3.9 (12)
France	17.7 %	31.0 %	69.5	66.3	4.8 (14)	6.5 (19)
Spain	8.2 %	15.3 %	68.1	61.3	4.9 (19)	6.7 (23)
Sweden	21.9 %	41.7 %	40.6	29.4	2.5 (8)	3.2 (11)
Italy	8.5 %	21.5 %	84.2	79.0	3.1 (24)	5.8 (38)
Greece	3.3 %	9.1 %	81.2	79.8	1.0 (9)	2.6 (21)
Portugal	11.6 %	28.3 %	67.9	66.8	2.0 (14)	4.7 (20)

Source: Kanavos 2014

Note: 1) volume-adjusted price indices for generics and patent-expired originator brands; 2) The analyzed countries were divided according to the perceived strength of their generic policies. Tier I (high): UK, Denmark, Germany, Netherlands, Finland, Tier II: Austria, France, Spain, Sweden, Tier III (low): Italy, Greece and Portugal.

The picture is similar for price developments: On average, in all countries prices declined, yet, there was significant variation with regard to magnitude and speed. The price decreases ranged from 59.4 % in Sweden to only 15.8 % in Italy one year after patent expiry.

While the differences of volume market shares and price developments between the countries do obviously not relate to the differences of country size, such a correlation applies to some extent with regard to the average number of competitors which was by far the highest in Germany and higher in France and Spain (not so in the UK, however).

In the literature, possible explanations for the considerable variations of generic competition and penetration in the European countries are discussed focusing on generic medicines policies. On the one hand, countries differ in supply-side policies, mainly with regard to prices (such as price capping, linking generic prices to the originator, or reference pricing systems). The EU pharma sector inquiry highlighted that policies involving price caps/mandatory discounts for generic medicines, while leading to (imposed) price decreases in the short term, in the longer run appear to lead to higher prices and to reduce the level of generic penetration relative to the regimes without price cap” (European Commission 2009, p. 86, 89). Moreover, there is some indication, that frequent adjustment of reimbursement levels or internal reference pricing has positively affected price competition and the degree of generic drug penetration (ibid.). However, such pricing policies do not seem to be an indispensable prerequisite for high generic penetration, as the comparison of Germany (with internal reference pricing) and the UK (with a liberal and open-market pricing system) shows (Kanavos 2014, p 238). Moreover, the reference pricing system in Germany has certainly contributed to establish and promote generic competition in the past, however, pricing pressure has been significantly increased in recent years by additional regulatory policies as combined co-payment exemptions and individual rebate contracts based on tendering – giving rise to concerns that this will promote oligopolization and price increases in the long run (cf. Albrecht/de Millas 2014). In the USA, on some substance markets prices have increased extraordinarily as manufacturers of generic drugs have legally obtained a market monopoly, caused – among other things – by drug shortages, supply disruptions, and limited competition (Alpern et al. 2014). Furthermore, oligopolization could result in a loss of diversity of supply and, thus, constrain the potential for individual pharmacotherapy.

On the other hand, countries also differ in their demand-side measures to promote generic utilization. Major demand-side approaches to promote generic competition are mandatory or strongly recommended prescription of active ingredient without indicating a specific supplier (i.e. INN prescribing) and/or mandatory generic substitution. Countries adopting such policies have shown the highest degree of generic penetration and also seem to have the lowest time delay to generic entry (Kanavos 2014, p 239). Consequently, demand-side measures to change physician prescribing habits are considered necessary to fully realize the benefits of generic medicines (Moon 2014).

4.1.2 Differences between substance groups

Variation of generic market penetration is not only a matter of differences in generic policies between countries, but also (and at least as distinct) a matter of differences between substances within a country. In fact, conditions of market entry and competition prove to be diverging depending on numerous factors such as patent litigation, controversies on potential medical differences, defence strategies of originators (offering generics themselves, rebate arrangements prior to patent expiry, “me too” strategies to reallocate demand) etc.

The differences of generic penetration between substance markets have recently been analyzed for Germany (Albrecht/de Millas 2014a). Categorizing substance markets with generic entry between January 2006 and June 2012 into three groups, average generic market share in terms of volume (DDD) for the time period 2006-2014 ranged from 94.1 % in the first group to only 17.7 % in group 3, two years after patent expiry in each case (Table 7). Group 1 with strong generic competition is also characterized by higher price decreases, particularly during the first year after patent expiry, strong increases of total market volume, temporary reduction in total sales, and a high number of competitors.

Table 7: Indicators of generic competition in Germany, 2006-2014

Germany	Ø market share generics (DDD) (grouping criterion)		Ø price change generics (% since market entry)		Ø change of total volume (DDD % since generic entry)		Ø change of total sales (% since generic entry)		Ø number of competitors	
	after	year 1	year 2	year 1	year 2	year 1	year 2	year 1	year 2	year 1
Group 1 with <u>functioning</u> generic competition	86.7%	94.1%	-60.4%	-61.7%	122.1% (63.9%)	230.0% (114.8%)	-12.1% (-19.1%)	6.9% (-7.6%)	21.6	21.7
Group 2 with <u>limited</u> generic competition	51.5%	67.5%	-40.0%	-52.0%	32.2%	39.7%	4.2%	-11.5%	12.0	18.0
Group 3 with <u>strongly</u> <u>limited</u> generic competition	10.9%	17.7%	-5.4%	-5.4%	18.5%	28.9%	18.3%	35.0%	2.6	3.3

Source: IGES based on NVI (Insight Health)

Note: substances with generic entry Jan 2006-June 2012; values in brackets: without Atorvastatin⁹

In contrast, group 3 substance markets had only small price decreases (-5.4 %), relatively moderate increases in total volume, increases in total sales, and only a small number of competitors.

⁹ Before patent expiry, Atorvastatin was assigned a reference price (“jumbo group”), however, its list price was above the reference price. As a consequence, its share of the SHI market for all statines was only about 1 %. This explains why there has been a dramatic increase of Atorvastatin’s market share after patent expiry.

With regard to market size, group 1 and group 2 dominated (comprising 19 substances each), however, 10 substances were assigned to group 3 with strongly limited generic competition. At the end of the time period analyzed (June 2014), group 3 substances' volume share (DDD) of all substances considered was only 7 %, but sales share was 22 %. Conversely, group 1 substances' volume share was 83 % as opposed to 37 % sales share.

4.2 Generic penetration, treatment utilization change, and cost-effectiveness

For the selected drug classes, generic market penetration and change in treatment utilization are looked at simultaneously. For reasons of data availability, this is done exemplarily for Germany.

For each substance of the group, the percentage change of the number of prescriptions and sales plus the generics' volume market share (based on prescriptions) are determined in the year of generic market entry and the two years before and after.¹⁰ Subsequently, these percentage changes for the individual substances are accumulated for each substance group, after weighting by the prescription share of the individual substance within its substance group.

The comparison of the development of volumes (based on prescriptions) on the one hand and sales on the other hand gives some first indications on changes in cost-effectiveness. Supplemented by the simultaneous change in the generics' volume market share, the relevance of the generic market entry for that development is highlighted. Finally, available evidence on the concrete effects generic medicines have on cost-effectiveness in terms of cost per quality-adjusted life-year (QALY) is presented.

The underlying expectation is that cost-effectiveness is improved along with generic market penetration (cf. Dylst et al. 2015). Functioning generic competition at patent expiry provided, prices decline significantly within the first two years, as has been observed for many substance markets in the past. This price decline increases cost-effectiveness by itself (*ceteris paribus*). In addition, the more expensive the comparator (originator's product) and the stronger the (clinical) health impact of the respective pharmacotherapy, the more the price decline increases cost-effectiveness.

Moreover, an increased cost-effectiveness facilitates medical prescription choices for physicians who have been partially hesitant to prescribe high-priced original or branded medicines. As a consequence, more and more previously untreated

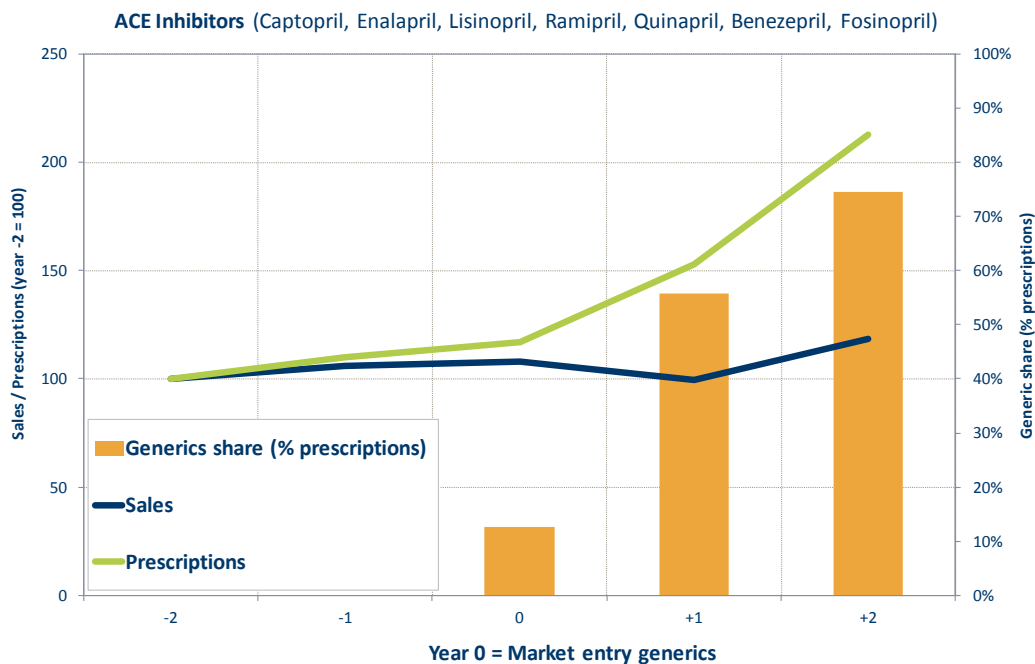
¹⁰ The underlying data is taken from Schwabe/Paffrath (various years) covering the time period from 1993 to 2014. Sales are calculated based on pharmacy list prices, for the years since 2011 reduced by mandatory discounts. Additional rebates from tenders are not deducted from sales. Depending on the relevant time period, sales were adjusted for changes in currency (2001: DM to Euro) and to changes of the value added tax rate (1992: 14%; 1993-1997: 15%; 1998-2006: 16%, since 2007: 19%).

patients may receive drug therapy from which they potentially benefit according to their medical indication and the respective treatment guidelines. Thus, generic penetration generates a positive impact on populations-based health outcomes.

4.2.1 Hypertension and antihypertensives

For antihypertensives, treatment utilization measured by the number of prescriptions increased considerably in Germany¹¹ after generic market entry, on average of all substances considered it almost doubled within two years (Figure 12). This marked increase of antihypertensive treatment was characterized by rapid generic market penetration: the volume market share (based on prescriptions) reached, on average, about three quarters two years after generic market entry. Sales, in contrast, kept almost stable, indicating that considerably more patients had been treated within two years after the respective generic market entry without noticeable rise in cost.

Figure 12: Change of generic market share and total prescriptions of anti-hypertensives (Germany)



Source: IGES based on data in Schwabe/Paffrath (various years)
 Note: changes of market shares and prescriptions weighted by prescription share of individual substance within substance group, accumulated over the respective reference points in time (year of patent expiry, 1 year after / 2 years after); individual rebates from tenders are not deducted from sales.

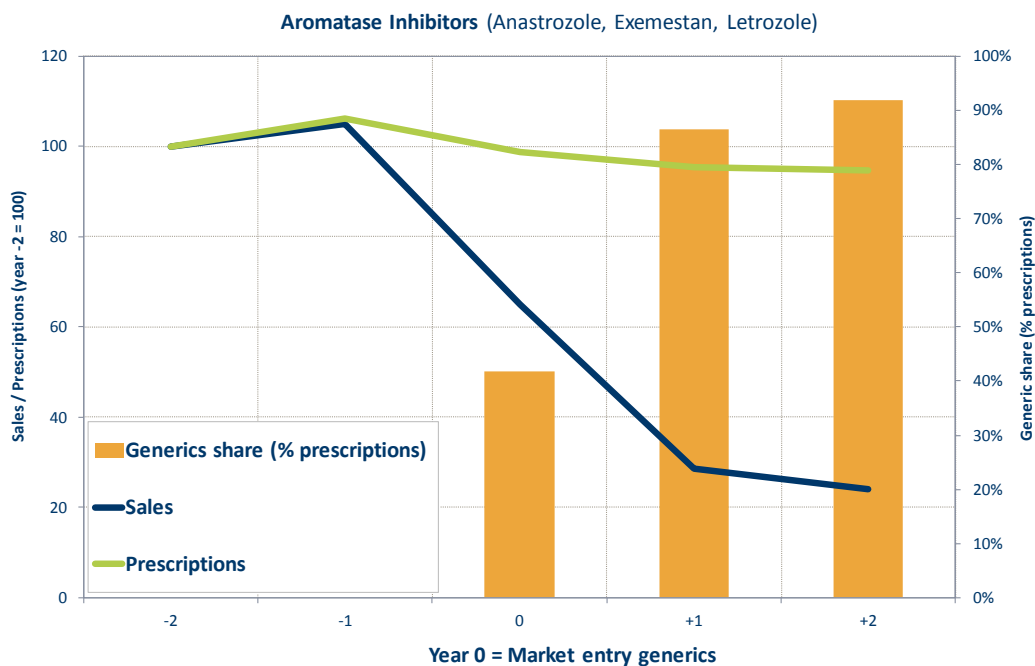
¹¹ Data refer to Social Health Insurance which covers about 90 % of total population.

The sharp increase of prescription volume with sales remaining almost stable after generic market entry can be seen as a first indication that cost-effectiveness has increased. Based on previous studies for the US population, Watanabe et al. (2014) estimated that cost of hypertension control medications for non-diabetic patients to gain an additional QALY versus non-treatment dropped by about 85 % when substituting available generic medications for brand medications (from \$52,983 to \$7,753).

4.2.2 Breast cancer and adjuvant endocrine therapy

The development of the drug market for adjuvant endocrine therapy around generic market entries shows an extraordinarily rapid generic penetration: generic volume market shares (based on prescriptions) reached, on average, more than 90 % two years after generic market entry (Figure 13). As opposed to the other two drug groups under consideration, treatment utilization measured by the number of prescriptions remained, on average, almost stable, in fact it decreased slightly. Thus, cost effectiveness of generic medicines is reflected here by a sharp decrease in sales.

Figure 13: Change of generic market share and total prescriptions of aromatase inhibitors (Germany)



Source: IGES based on data in Schwabe/Paffrath (various years)

Note: changes of market shares and prescriptions weighted by prescription share of individual substance within substance group, accumulated over the respective reference points in time (year of patent expiry, 1 year after / 2 years after); individual rebates from tenders are not deducted from sales.

As opposed to other substance markets (e.g. antihypertensives) generic market entry and penetration did not boost treatment utilization in the case of aromatase inhibitors in Germany. This is due to the fact that in more comprehensive health systems with access free of charge like Germany, breast cancer is treated as an instantly life-threatening disease. So there is barely any medical need which is not further met until generic medicines become available as can be observed for many other indications. The slight decrease in prescriptions of aromatase inhibitors in Germany may be attributable to improved screening and early detection which was accompanied by declining morbidity rates in 2009-2010.¹²

An almost constant treatment utilization level accompanied by a sharp decline in sales may be seen a first indication for increased cost-effectiveness. For Germany, the change of incremental cost per QALY has been estimated for endocrine therapies in the adjuvant setting for postmenopausal patients with hormone receptor-positive breast cancer, particularly taking into account the potential of generic medicines prices (Lux et al. 2011). The study calculated the cost-effectiveness ratio of treatment with letrozole and anastrozole, each compared to tamoxifen. Assuming different levels of the original price reductions by generic medicines, the cost-benefit modeling yielded a decline of incremental cost per QALY compared with tamoxifen ranging from almost 30 % (with 25 % price reduction) to 87 %-89 % (with 75 % price reduction).

4.2.3 Depression and antidepressants

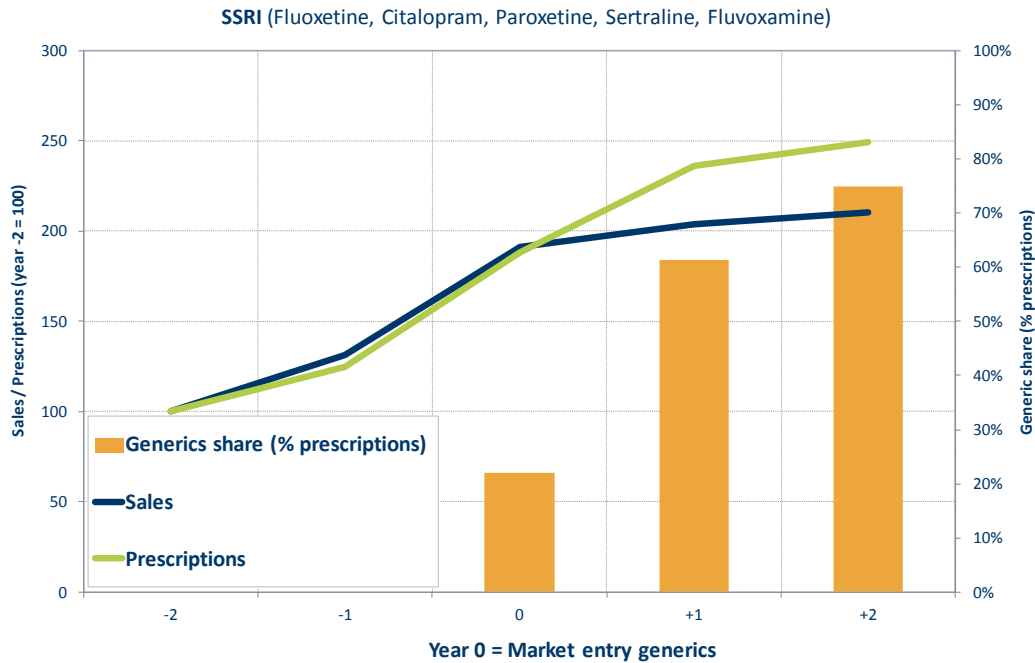
Utilization of SSRI treatment of depression measured by the number of prescriptions rose considerably during the reference time periods, on average by one and a half times (The utilization increase was accompanied by a distinct shift in market shares so that the generic SSRI reached, on average, about three quarters of prescription volumes two years after their market entry. The effect of generic competition in the SSRI market is primarily reflected by the flattening of the sales curve (particularly during the first year after generic market entry). That means that the continuous utilization increase could be realized at relatively lower cost.

Figure 14). However, this average increase has been driven not only by generic market entry, because it spread over the entire observation period and includes the years before generic market entry.

The utilization increase was accompanied by a distinct shift in market shares so that the generic SSRI reached, on average, about three quarters of prescription volumes two years after their market entry. The effect of generic competition in the SSRI market is primarily reflected by the flattening of the sales curve (particularly during the first year after generic market entry). That means that the continuous utilization increase could be realized at relatively lower cost.

¹² http://www.rki.de/Krebs/DE/Content/Krebsarten/Brustkrebs/brustkrebs_node.html

Figure 14: Change of generic market share and total prescriptions of SSRI (Germany)



Source: IGES based on data in Schwabe/Paffrath (various years)

Note: changes of market shares and prescriptions weighted by prescription share of individual substance within substance group, accumulated over the respective reference points in time (year of patent expiry, 1 year after / 2 years after); individual rebates from tenders are not deducted from sales.

The frequent observation on German drug markets that generic market entry and penetration boost treatment utilization, seems to be superimposed by other factors in the case of SSRI: While the number of patients with diagnosed depression keeps rising in many countries, it is estimated that “real” prevalence of major depression was stable in the EU between 2005 and 2011 (12month prevalence: 6.9 % corresponding to 30.3 million persons affected in the EU 2011) (Wittchen et al. 2011, p 663). However, the crucial factor driving treatment utilization up is low treatment rates. According to convergent findings of several national and regional studies, only half of all patients with a mental disorder has ever received some treatment, and even considerably fewer (10 %) receive notionally adequate mental health care by drugs or psychotherapy, suggesting a substantial level of unmet needs (see *ibid.*, p 671). Besides, mental disorders are extremely costly because of indirect cost; among mental disorders, unipolar depression has the highest DALY¹³ rate per 10,000 persons (*ibid.*, p 669).

¹³ DALY (Disability Adjusted Life Years) captures years of life lost due to premature mortality and due to living with disability.

5. Conclusion

In the traditional perspective on generic medicines, emphasis is put on their **overall economic value**. Generic medicines contribute substantially to drug supply. In some European countries, their volume market shares reach 80 %, whereas their respective share of market value is usually much lower indicating their cost-reducing effects to the benefit of health care systems. However, there are considerable country variations in uptake of generic medicines leading to differences with regard to both volume market shares and to the discrepancy between volume and value shares, due to different institutional settings and policies to promote generic substitution. Price decreases are the primary indicator of cost savings caused by generic market entry. In recent years, prices have declined up to 70 % on average within two years after generic market entry, depending on country and on substance group. Considerable country variations among EU member states, again, indicate that savings potential has not been fully exploited yet.

The focus of the present study is – beyond these overall economic dimensions – on the **patient-related value** of generic medicines which was examined in more detail for three selected drug classes: antihypertensives, adjuvant endocrine therapies, and antidepressants. For all of them, there is clinical evidence that patients benefit from drug treatment being reflected in observable improvements of population-based health outcomes which, in turn, are accompanied by increasing, or at least continuous, utilization of drug treatments. Based on data for Germany, the crucial role of **patient access** to generic medicines and of rapid generic market penetration is highlighted, both being the precondition for achieving both cost savings and health impact.

For **antihypertensives**, there is comprehensive evidence on the clinical benefit due to lowering of blood pressure and, consequently, to reducing the risks of stroke, coronary heart disease, heart failure or cardiovascular death. There is, moreover, evidence that these benefits are largely independent of the drugs employed, with regard both to drug classes and to original branded drugs or its generic equivalents. Utilization of hypertension drugs has increased considerably over the last decades in European countries. At the same time, hypertension-related mortality has decreased significantly in the EU countries (in Germany, for example, by about 50 % between 1998 and 2010). One of the designated causes for the observed mortality decline is better medicinal treatment options, though other factors also contributed (such as smoking reduction, better hypertension control, guideline implementation). For Germany, it could be shown that treatment utilization increased significantly after generic market entry, combined with rapid generic market penetration. Sales, in contrast, kept almost stable, indicating that considerably more patients had been treated within two years after the respective generic market entry without noticeable rise in cost, suggesting an increase in cost-effectiveness. Correspondingly, based on US-data it was estimated that generic substitution brings cost of hypertension control medications to gain an additional QALY down by about 85 %.

With regard to **adjuvant endocrine therapies** to treat breast cancer, there is clinical evidence that mortality is reduced by a third and recurrence rates by almost 40 % over 15 years after treatment start. The clinical benefit differs between drug classes, yet primarily depending on the patient's menopausal status. Utilization of endocrine therapies increased or remained steady over the past decade, while breast cancer-related mortality decreased in European countries, in many of which by about a quarter up to a third. Besides improved treatment options, early detection programs have also contributed to this reduction. German data show extraordinary rapid generic penetration with generic volume market shares reaching, on average, more than 90 % two years after generic market entry. As a result, sales declined substantially while treatment utilization remained almost at constant levels, suggesting significantly increased cost-effectiveness. This has been confirmed by study estimations, showing that price reductions by generic medicines which can reasonably be expected lead to a decline of incremental cost per QALY (AI vs. SERM) ranging from almost 30 % to almost 90 %.

Clinical evidence for **antidepressants** with regard to the treatment goals of remission, prevention of relapse, and prophylactic treatment is more heterogeneous. Antidepressant drugs seem to be more effective than placebo in the treatment of major depression, whereas in patients with mild depressive episodes, they have often proved not to be more effective than placebo. Different substances are generally equally effective, yet, there are significant differences in toxicity and side effects. Utilization of antidepressant treatment has still increased considerably over the last decade, as treatment of depression has become socially more acceptable and the willingness to seek treatment has increased. As opposed to the other drug groups examined, there are no comparably obvious health outcome indicators for depression. A possible indicator is the rate of suicides as a type of depression-related mortality. In fact, death rates caused by suicide have decreased significantly in many European countries. However, evidence on whether and how much antidepressants contribute to a reduction of suicides or rather increase the risk of suicidal behaviour is ambiguous. Alternative health benefit indicators with regard to antidepressant treatment (such as the reduction of work disability) have been rarely considered yet. The fact that treatment utilization has increased substantially regardless of relatively limited clinical and population-based evidence on health benefits is attributable to the large share of still untreated or inadequately treated patients and, thus, to unmet medical need.

The three selected drug classes illustrate – based on the German example – different variations on how generic medicines contribute to positive health impact: Rapid generic market penetration reaching volume market shares between 75 % and 90 % two years after generic market entry

- ◆ facilitated a considerable increase of utilization by keeping sales stable, thus increasing cost-effectiveness (antihypertensives),

- ◆ facilitated continued increase of utilization by dampening sales, thus counteracting the problem of low treatment rates (antidepressants),
- ◆ sharply decreased sales with steady treatment utilization, thus substantially reducing incremental cost per QALY (adjuvant endocrine therapies).

Besides increasing cost-effectiveness, patient access to generic medicines may improve treatment **adherence** and, thus, cause positive health impact. High(er) co-payments for branded medicines, but also education measures for patients referring to generic substitution support a positive impact of generic medicines on patient adherence. However, the process of generic substitution is also prone to negatively influence patient adherence, as the controversial discussion about the effects of individual rebate contracts on patient compliance in Germany illustrates. Correspondingly, findings for the three selected drug groups are inconsistent. For antihypertensives, generic drugs have been associated both with positive and negative impact on adherence. For generic aromatase inhibitors, available evidence for the USA shows positive associations with adherence whereas higher prescription co-payments were associated with non-adherence and discontinuation of AIs. For antidepressants, there is evidence (again for the USA) for both that generic initiation of treatment was associated with lower hazard rate of treatment disruption and that discontinuation rates did not differ significantly among patients using brand versus generic SSRI or SNRI.

Further research should be intensified with regard to the patient-related value of generic medicines. This involves, first, detailed estimation of improved cost-effectiveness for further indication areas or patient groups. Beyond that, the specific contribution of generic medicines to the reduction of unmet medical need, or of the number of untreated or inadequately treated patients respectively, could be examined in more detail. Finally, additional health outcome indicators related to (generic) drug therapy should be considered in future research, such as the reduction of work disability.

Literature

- Albrecht M, de Millas C (2014): Die Bedeutung von Rabattverträgen für den Generikawettbewerb (The importance of rebate contracts for the competition in the generic market). In: *pharmind® – die pharmazeutische industrie*, Vol. 76, 4: 526-531
- Albrecht M, de Millas C (2014a): Analyse des Generikawettbewerbs (2005-2014), Aktualisierung der Analyse aus dem Jahr 2011 im Auftrag von Pro Generika (Analysis of generic competition 2005-2014, update of 2011 analysis on behalf of Pro Generika) (unpublished)
- Alpern JD, Stauffer WM, Kesselheim AS (2014): High-Cost Generic Drugs – Implications for Patients and Policymakers, in: *The New England Journal of Medicine*, 371; 20: 1859-1862.
- Autier P, Boniol M, LaVecchia C, Vatten L, Gavin A, Héry C & Heanue M (2010): Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. In: *BMJ*, 341: c3620. DOI: 10.1136/bmj.c3620.
- Barbui C, Furukawa T A, Cipriani A (2008): Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *Canadian Medical Association Journal* 178: 296-305.
- Bao Y, Ryan AM, Shao H, Pincus HA & Donohue JM (2013): Generic Initiation and Adherence to Antidepressant Therapy under Medicare Part D. *American Journal of Managed Care*, Vol. 19, 12: 989-998.
- Briesacher BA, Gurwitz JH & Soumerai SB (2007): Patients At-Risk for Cost-Related Medication Nonadherence: A Review of the Literature. In: *Journal of General Internal Medicine*, 22: 864-871. DOI: 10.1007/s11606-007-0180-x.
- Briesacher BA, Andrade SE, Fouyazi H, Chan KA (2009): Medication Adherence and the Use of Generic Drug Therapies. In: *American Journal of Managed Care*, Vol. 15, 7: 450-456.
- Burstein HJ, Griggs JJ, Prestrud AA & Temin S (2010): American Society of Clinical Oncology Clinical Practice Guideline Update on Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer. In: *Journal of Oncology Practice*, Vol. 5, 6: 243-246. DOI: 10.1200/JOP.000082.
- Busse R, Panteli D, Henschke C (2015): Arzneimittelversorgung in der GKV und 15 anderen europäischen Gesundheitssystemen, Ein systematischer Vergleich (Pharmaceutical supply in the German SHI and 15 other European health systems, a systematic comparison), TU Berlin, Working papers in health policy and management Band 11.
-

- Cassel D, Ulrich V (2012): Einsparpotenziale in der GKV-Arzneimittelversorgung, Zur Belastbarkeit von Potenzialberechnungen als Richtschnur für eine rationale Regulierung des Arzneimittelmarktes, Gutachten für den Bundesverband der Pharmazeutischen Industrie e.V. (BPI) (Savings potential in SHI drug supply, On the reliability of potential calculations as guideline for a rational regulation of the drug market, Expertise for the Federal Association of the Pharmaceutical Industry).
- Cifková R et al. (2010): Longitudinal trends in cardiovascular mortality and blood pressure levels, prevalence, awareness, treatment, and control of hypertension in the Czech population from 1985 to 2007/2008. *Journal of Hypertension* 28(11):2196-203. doi: 10.1097/HJH.0b013e32833d4451.
- Collins R, MacMahon S (1994): Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease, in: *British Medical Bulletin*, Vol. 50, 2: 272-298
- Colombo GL, Agabiti-Rosei E, Margonato A, Menacci C, Montecucco CM & Trevisan R (2013): Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy. In: *PLoS ONE*, Vol. 8, 12: e82990. DOI:10.1371/journal.pone.0082990.
- Corrao G, Soranna D, La Vecchia C, Catapano A, Agabiti-Rosei E, Gensini G, Merlino L & Mancina G (2014) : Medication persistence and the use of generic and brand-name blood pressure-lowering agents. In: *Journal of Hypertension*, Vol. 32, 5: 1146-1153. DOI: 10.1097/HJH.0000000000000130.
- Dylst P, Vulto A, Simoens S (2015): Societal value of generic medicines beyond cost-saving through reduced prices, in: *Expert Review of Pharmacoeconomics & Outcomes Research*, DOI: 10.1586/14737167.2015.1017565.
- Eaddy MT, Cook CL, O'Day K, Burch SP & Cantrell CR (2012): How Patient Cost-Sharing Trends Affect Adherence and Outcomes: A Literature Review. In: *Pharmacy and Therapeutics*, Vol. 37, 1: 45-55.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. In: *The Lancet*, 2005, Vol. 365: 1687-1717.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2011): Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. In: *The Lancet*, Vol. 378, 9793: 771-784. DOI: 10.1016/S01406736(11)609938.
- Estoppey D, Paccaud F, Vollenweider P, Marques-Vidal P (2011): Trends in self-reported prevalence and management of hypertension, hypercholesterolemia and diabetes in Swiss adults, 1997-2007, *BMC Public Health* 2011, 11:114, <http://www.biomedcentral.com/1471-2458/11/114>
-

- European Society for Medical Oncology (ESMO) (2013): Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. In: *Annals of Oncology*, 24, 6: vi7–vi23, 2013. DOI:10.1093/annonc/mdt284.
- European Commission, Competition DG: Pharmaceutical Sector Inquiry, Final Report, 8 July 2009.
- European Federation of Pharmaceutical Industries and Associations (EFPIA) (2014): The pharmaceutical industry in figures. Key data 2014.
- European Generic medicines Association (EGA) (2015): EGA Fact Sheet on generic medicines.
- European Society of Hypertension (ESH) & European Society of Cardiology (ESC) (2013): 2013 ESH/ESC Guidelines for the management of arterial hypertension. In: *Journal of Hypertension*, 31: 1281-1357. DOI: 10.1097/01.hjh.0000431740.32696.cc
- Furukawa T A, Streiner D L, Young L T (2001): Antidepressant plus benzodiazepine for major depression. *Cochrane Database of Systematic Reviews 2*: CD001026.
- Hakonsen H, Toverud EL (2012): A review of patient perspectives on generics substitution: what are the challenges for optimal drug use. In: *GaBI Journal*, Vol. 1, 1: 28-32.
- Häussler B, Höer A & de Millas C (ed.) (2015): *Arzneimittel-Atlas 2015: Der Arzneimittelverbrauch in der GKV (Pharmaceutical Atlas 2015: The drug consumption in the German SHI system)*, Berlin.
- Haustein R, de Millas C. (2010) Gründe für Änderungen im Verschreibungsverhalten von Ärzten. (Motives for changes in prescription behaviour of physicians) In: *Infrastruktur Recht (IR) Energie, Verkehr, Abfall, Wasser*, Vol. 7, 11: 327-330
- Hershman DL, Tsui J, Meyer J, Glied S, Hillyer GC, Wright JD & Neugut AI (2014): The Change From Brand-Name to Generic Aromatase Inhibitors and Hormone Therapy Adherence for Early-Stage Breast Cancer. In: *Journal of the National Cancer Institute*, Vol. 106, 11. DOI:10.1093/jnci/dju319.
- IMS Institute for Healthcare Informatics (2015): The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective. https://www.imshealth.com/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Insights/IIHI_Generics_Healthcare_Brief.pdf
- IMS (2010): Einfluss von Rabattverträgen auf die Arzneimittelversorgung, BAH-Studie 2010 (Effect of rebate contracts on pharmaceutical supply, study for the Federal Association of pharmaceutical manufacturers).
- Isacsson G, Reutfors J, Papadopoulos FC, Ösby U & Ahlner J (2010): Antidepressant medication prevents suicide in depression. In: *Acta Psychiatrica Scandinavica*, 122: 454-460. DOI: 10.1111/j.1600-0447.2010.01561.x
-

- Kanavos P (2014): Measuring performance in off-patent drug markets: A methodological framework and empirical evidence from twelve EU Member States, *Health Policy* 118, 229-241.
- Kanavos P, Nicod A F E, Sandberg D (2012): Tender systems for outpatient pharmaceuticals in the European Union: Evidence from the Netherlands and Germany, Study for the European Commission – DG Enterprise. October 2012. http://progenerika.de/wp-content/uploads/2013/02/Anlage-2_Tendering-Report-EMINET-13OCT2012-FINAL.pdf
- Kelly E, Lu CY, Albertini S & Vitry A (2015): Longitudinal trends in utilization of endocrine therapies for breast cancer: an international comparison. In: *Journal of Clinical Pharmacy and Therapeutics*, 40: 76-82. DOI: 10.1111/jcpt.12227.
- Kendrick T et al. (2009): Randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of selective serotonin reuptake inhibitors plus supportive care, versus supportive care alone, for mild to moderate depression with somatic symptoms in primary care: the THREAD (THREShold for AntiDepressant response) study. *Health Technology Assessment* 13: iii – xi, 1.
- Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK & Shrank WH (2008): Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis. In: *Journal of the American Medical Association*, Vol. 300, 21: 2514-2526. DOI: 10.1001/jama.2008.758.
- Leucht S (2012): Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *The British Journal of Psychiatry* 200: 97-106.
- Lux MP et al. (2011): Cost-Benefit Analysis of Endocrine Therapy in the Adjuvant Setting for Postmenopausal Patients with Hormone Receptor-Positive Breast Cancer, Based on Survival Data and Future Prices for Generic Drugs in the Context of the German Health Care System. In: *Breast Cancer* 6: 381-289, DOI: 10.1159/000333118.
- Melander H et al. (2008): A regulatory Apologia – a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *European Neuropsychopharmacology* 18: 623-627.
- Mennini F S et al. (2015): Cost of poor adherence to anti-hypertensive therapy in five European countries, in: *The European Journal of Health Economics* 16 (1), DOI: 10.1007/s10198-013-0554-4.
- Moon JC et al. (2014): Different initiatives across Europe to enhance losartan utilization post generics: impact and implications, in: *frontiers in Pharmacology*, Vol. 5, Article 219, DOI: 10.3389/fphar.2014.00219.
- OECD (2013): *Health at a Glance 2013: OECD Indicators*. OECD Publishing. DOI: 10.1787/health_glance-2013-en
-

- Rathe J, Andersen M, Jarbøl DE, dePont Christensen R, Hallas J, Søndergaard J (2015): Generic Switching and Non-Persistence among Medicine Users: A Combined Population-Based Questionnaire and Register Study. PLoS ONE, Vol. 10(3), e0119688. DOI:10.1371/journal.pone.0119688.
- Robert Koch Institut (RKI) (2015): Der Blutdruck in Deutschland ist gesunken, das Präventionspotenzial bleibt aber hoch (Blood pressure has declined in Germany, potential for prevention remains high). In: Epidemiologisches Bulletin, Nr. 5, 33-40.
- Roebuck MC et al. (2011): Medication adherence leads to lower health care use and costs despite increased drug spending. Health Aff (Millwood) 2011 Jan;30(1): 91-9.
- Schwabe U, Paffrath D (ed). (2014) Arzneiverordnungs-Report 2014: Aktuelle Daten, Kosten, Trends und Kommentare (Drug Prescription Report 2014: Current data, cost, trends and comments). Berlin, Heidelberg: Springer-Verlag (plus older editions 1993-2013)
- Seifert C, Lottmann K, Chen X, Gulyaev D, Rosenfeld S, Schädlich PK & Müller E (2011): Budget-Impact-Analyse von Dronedaron bei Behandlung von Patienten mit nicht-permanentem Vorhofflimmern aus Perspektive der GKV in Deutschland (Budget-Impact Analysis of Dronedaron for the Treatment of Patients with non-permanent Atrial Fibrillation from the Perspective of the German Statutory Health Insurance). Perfusion 24(6), 212-220.
- Storosum J G et al. (2001): Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic study. European Neuropsychopharmacology, 11: 173-180.
- Turnbull F (2003): Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. In: The Lancet, Vol. 362, 9395: 1527-1535.
- Vlahiotis A, Devine ST, Eichholz J, Kautzner A (2011): Discontinuation Rates and Health Care Costs in Adult Patients Starting Generic Versus Brand SSRI or SNRI Antidepressants in Commercial Health Plans. In: Journal of Managed Care Pharmacy, Vol. 17, 2: 123-132.
- Watanabe JH, Hazlet TK, Sullivan SD (2014): Generic medication utilization policies in the United States and Medicaid sustainability, in: Journal of Pharmaceutical Health Services Research, 6: 3-10.
- Van Wijk BLG, Klungel OH, Heerdink ER & de Boer A (2006): Generic Substitution of Antihypertensive Drugs: Does It Affect Adherence? In: The Annals of Pharmacotherapy, Vol. 40: 15-20. DOI: 10.1345/aph.1G163.
- Wissenschaftliches Institut der AOK (WIdO) (2011): AOK-Arzneimittelrabattverträge: Mehr Therapiesicherheit für Patienten (Rebate contracts for drugs by AOK sickness funds: more treatment safety for patients), <http://www.wido.de/meldungakt+M5e4ef7c7814.html>
-

Wittchen H U et al. (2011): The size and burden of mental disorders and other disorders of the brain in Europe 2010, *European Neuropsychopharmacology* 21, 655-679. doi:10.1016/j.euroneuro.2011.07.018.

World Federation of Societies of Biological Psychiatry (WFSBP) (2013): World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. In: *The World Journal of Biological Psychiatry*, 14: 334-386. DOI: 10.3109/15622975.2013.804195
