Psychopharmacology (2011) 216:579–587
DOI 10.1007/s00213-011-2256-x

ORIGINAL INVESTIGATION

Effectiveness and costs of flupentixol compared to other first- and second-generation antipsychotics in the treatment of schizophrenia

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Received: 13 February 2011 / Accepted: 28 February 2011 / Published online: 25 March 2011

Abstract
Rationale The purpose of this study is to analyse the effectiveness of flupentixol compared to other first- and second-generation antipsychotics for the treatment of schizophrenia in routine care.
Method A retrospective cohort study was conducted using administrative data from four sickness funds covering 12.6 million insured. Patients discharged from hospital in 2003 with an ICD-10 diagnosis of schizophrenia were followed for 12 months. Rehospitalisation during follow-up was analysed using a hurdle regression model. Treatment costs were defined as cost of pharmaceutical and cost of inpatient care. Two thousand eight hundred ninety insured were included, of which 177 were treated with flupentixol during follow-up, while 429 and 2,284 were treated with other first-and second-generation antipsychotics, respectively.
Results Compared to patients treated with flupentixol (21.0 days), predicted hospitalisation did not differ significantly for patients treated with other first- (21.3 days, $p=0.8313$) or second-generation antipsychotics (25.6 days, $p=0.4035$). Predicted treatment costs for the average patient were 4,193 € if treated with flupentixol, 4,846 € if treated with other first-generation antipsychotic, and 6,523 € if treated with a second-generation antipsychotic. Second-generation antipsychotics showed a clear advantage over flupentixol concerning extrapyramidal symptoms co-medication.
Conclusion The effectiveness of flupentixol preventing relapse in patients with schizophrenia appears to be similar to that of other first- and second-generation antipsychotics. However, the low treatment costs for patients treated with flupentixol could be explained by the small number of patients with readmissions (70 insured) and the larger share of patients treated with its depot formulation.

Keywords Flupentixol · Atypical antipsychotics · Schizophrenia

Introduction

Schizophrenia is a common psychiatric disorder with a lifetime prevalence of approximately 4 in 1,000 inhabitants (Saha et al. 2005). The disease is characterised by a broad range of mental and neuropsychological dysfunctions including thinking, perception of reality, ideation, concentration and motivation, in addition to hallucinations and delusional beliefs. Additional complex symptoms include social isolation, an inability to make decisions, and poor self-care. The early onset of the disease (usually in the 20s), chronic nature of the illness in one third of patients and the incidence of repeated episodes of schizophrenia in about 70% of affected individuals compounded by a temporary or permanent inability to work make the disease very cost

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intensive (Kissling et al. 1999; Haro et al. 2003). Therefore, prevention of relapse and avoidance of a chronic course of illness are important therapeutic goals.

Current evidence suggests that second-generation antipsychotic (SGA) drugs are more efficacious than first-generation antipsychotics in preventing relapse, which may lead to higher acceptance by patients (Tollefson et al. 1997; Csernansky et al. 2002; Davis et al. 2003; Zhang et al. 2004). However, these claims have been questioned in some of the recent studies (Geddes et al. 2000; Rosenheck et al. 2003; Sernyak et al. 2003; Lieberman et al. 2005; Jones et al. 2006; Stargardt et al. 2008). On the one hand, the second-generation antipsychotics have a more favourable side-effect profile regarding extrapyramidal symptoms (EPS), which, in turn, may lead to improved therapy adherence (Crossley et al. 2010). On the other hand, another key concern in the debate about the differential efficacy and effectiveness of first- versus second-generation antipsychotics has been the substantially higher costs of second-generation antipsychotic drugs. Based on limited data from one randomised clinical trial by Tollefson et al. (1997), it has been claimed that these could be offset by the higher efficacy of the second-generation antipsychotics to reduce rehospitalisation, leading to cost savings for inpatient care.

Regarding this background, flupentixol might be a possible compromise treatment option. Current evidence suggests that flupentixol has first- and second-generation characteristics and probable beneficial effects in patients with predominantly negative symptoms (Kühn et al. 2000; Müller et al. 2002; Philipp et al. 2003; Hertling et al. 2003; Gattaz et al. 2004). We therefore compared the effectiveness and costs of patients treated with flupentixol with other first- and second-generation antipsychotics in a real world setting using routine data from four German sickness funds (Techniker Krankenkasse, AOK Baden-Wuerttemberg, AOK Westfalen-Lippe and AOK Berlin).

Materials and methods

Study design

Insured members from four German sickness funds (Techniker Krankenkasse, AOK Baden-Wuerttemberg, AOK Westfalen-Lippe and AOK Berlin) who had been hospitalised with a diagnosis of schizophrenia (ICD-10 'F20') were followed up for 12 months after their first discharge from hospital in 2003. To determine exposure, prescription data for antipsychotics were collected for each patient during follow-up.

Subsequently, patients were classified into three different groups according to the antipsychotic drug treatment received in the outpatient sector. It was differentiated between those treated with flupentixol, those treated with other first-generation antipsychotic drugs and those treated with second-generation antipsychotic drugs. Patients who switched medication during follow-up, either within a drug class or between different classes, were excluded from the main analyses. However, switching rates within classes were reported as they constitute an important outcome.

Outcome measures

As in previous effectiveness studies, mean hospital bed days and rehospitalisation rates during follow-up were chosen as the main outcome parameters for this study (Conley et al. 1999; Conley et al. 2003; Tiihonen et al. 2006). Costs of treatment, defined as cost of inpatient care, cost of antipsychotic treatment and cost of other pharmaceutical treatment from the payer's perspective, were also compared. In addition, medications commonly used to treat disease and medication-related side effects were collected. These included prescriptions for anticholinergics and the neuroleptic tiapride to treat extrapyramidal symptoms, anxiolytics to treat anxiety, and prescriptions for hypnotic and sedative drugs to treat insomnia or agitation.

Covariates

To control for possible bias or confounding by severity of disease, data on prior hospitalisations with a diagnosis of schizophrenia were collected for 2000, 2001 and 2002. A severity index was constructed dividing the number of days in hospital with an ICD-10 diagnosis of F20.X in 2000, 2001 and 2002 by days of membership with the sickness fund. The ratio was multiplied by 365 resulting in a severity index expressed as mean prior days hospitalised due to schizophrenia per year. In addition data on age and gender were obtained from the database.

Statistical analysis

We hypothesised that outcome measures were a function of medication, age, gender and prior hospitalisation due to schizophrenia in 2000, 2001 and 2002. Rehospitalisation during follow-up was analysed using a hurdle regression model. A hurdle regression model is a two part model, i.e. it treats the data in two steps. First, the probability to get hospitalised is estimated (inflation part of the model). Second, for the group of patients who were hospitalised, the number of days hospitalised was predicted assuming a Poisson distribution (Poisson regression model). Differences in treatment costs, defined as cost of pharmaceutical and cost of inpatient care, were analysed assuming a gamma distribution for treatment costs. A log link function

was employed. The probability to receive one of the three co-medications commonly used to treat disease and medication-related side effects (anticholinergics and tiapride to treat extrapyramidal symptoms, anxiolytics to treat anxiety, and prescriptions for hypnotic and sedative drugs to treat insomnia or agitation) were analysed using logistic regression models. For all models, it was tested for interactions and non-linear effects. Predicted outcome measures were calculated for 0, 20, 50 and 80 days of annual prior hospitalisation, respectively. To calculate predicted outcome measures, a patient with average age and mode gender was assumed. Statistical analysis was conducted using SAS version 9.1.

Sensitivity analysis

As a sensitivity analysis, we included a variable for depot use in all models in two ways: (a) as a dummy variable indicating if at least one prescription of an antipsychotic had been for a depot and (b) a continuous variable measuring the percentage of depot use among antipsychotic prescriptions. As the results for second-generation antipsychotics may be influenced by the large group of patients receiving clozapine, a drug associated with less side effects, we differentiated between patients that received clozapine and those who received other second-generation antipsychotics.

Results

In 2003, 11,688 insured members were hospitalised at least once with schizophrenia, and 1,159 patients were excluded because their membership with the sickness fund ended during follow-up. Another 350 insured were excluded because their membership with the sickness fund was less than 365 days between 2000 and 2002. In addition, 1,637 insured from one of the sickness fund had to be excluded because of incomplete membership data. Twenty-six patients were excluded because they were below 16 years of age, and 3467 patients were excluded because of being treated with a combination of first- and second-generation antipsychotics, as well as 747 patients who had no record of prescriptions in the outpatient sector.

Three thousand forty patients were treated with second-generation antipsychotics only (thereof 756 switchers within class, 24.9% of subgroup), and 1356 patients were treated with first-generation antipsychotics (thereof 750 switchers within class, 48.9%). Of the 606 non-switchers treated with first-generation antipsychotics, 177 were treated with flupentixol (see Table 1, Fig. 1). After excluding switchers, the final study population comprised 2,890 patients with a mean age of 40.4 years (range, 16 to 90 years), 1,586 insured (54.9%) were male while 1,304 (45.1%) were female (for characteristics by medication subgroup see Table 2).

Table 1 Study population by antipsychotic medication

	Number of patients	% of subgroup	% of study population
Second-generation antipsychotics (non-switchers)	2,284		
Olanzapine	650	28.5	22.5
Risperidone	548	24.0	19.0
Clozapine	476	20.8	16.5
Amisulpride	302	13.2	10.4
Quetiapine	218	9.5	7.5
Ziprasidone	83	3.6	2.9
Zotepine	7	0.3	0.2
Flupentixol	177	100.0	6.1
All other first-generation antipsychotics	429		14.8
Haloperidol	162	37.8	5.6
Perazine	80	18.6	2.8
Fluphenazine	58	13.5	2.0
Zuclopenthixol	25	5.8	0.9
Promethazine	17	4.0	0.6
Perphenazine	15	3.5	0.5
Melperone	13	3.0	0.4
Chlorprothixene	10	2.3	0.3
Sulpiride	10	2.3	0.3
Pipamperone	9	2.1	0.3
Benperidole	8	1.9	0.3
Fluspirilene	7	1.6	0.2
Levomepromazine	6	1.4	0.2
Bromperidole	3	0.7	0.1
Pimozide	2	0.5	0.1
Thioridazine	2	0.5	0.1
Prothipendyle	2	0.5	0.1

Hospitalisation

During follow-up, 1,195 patients (41.3% of the study population) were hospitalised at least once. The average number of hospitalisations was 0.77 (range, 0 to 15) per year with a mean duration of 28.1 days (range, 1 to 354). Compared to patients treated with flupentixol, the likelihood of hospitalisation for patients treated with other first- (p=0.4035) or second-generation antipsychotics (p=0.8313) did not differ significantly. If hospitalised, the number of days hospitalised was lower for patients treated with flupentixol compared to patients treated with other first- (p<0.0001) or second-generation antipsychotics (p<0.0001) (see Table 3 and Fig. 2). Hospitalisation for the average patient (age= 40.4 years, male, prior hospitalisation 22.7 days) was 21.0,

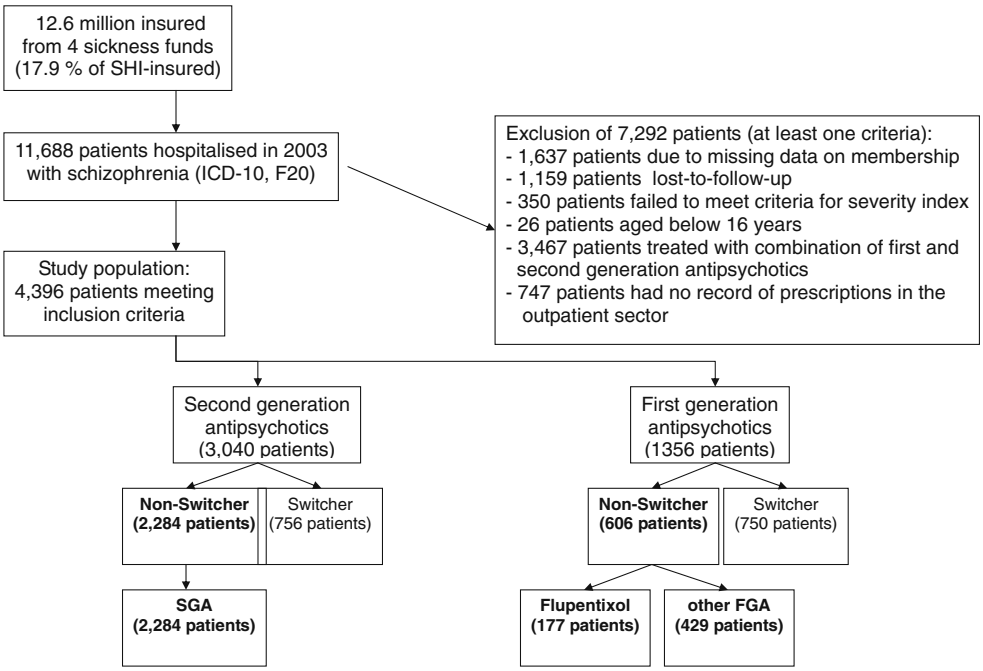

Fig. 1 Study population

21.3 and 25.6 if treated with flupentixol, first- or second-generation antipsychotic, respectively.

Treatment costs

Treatment costs were mainly driven by inpatient expenditure. Predicted treatment costs for the average patient (age= 40.4 years, male, prior hospitalisation 22.7 days per year) were 4,193 € if treated with flupentixol, 4,846 € if treated with other first-generation antipsychotic and 6,523 € if treated with a second-generation antipsychotic (see Fig. 3). Differences in treatment costs between second-generation antipsychotics and flupentixol were significant ($p<0.0001$) while difference in treatment costs between flupentixol and first-generation antipsychotics were not ($p=0.0829$).

Prescriptions against disease and medication-related effects

With regard to side effects, 20.3% of patients treated with flupentixol received prescriptions for anticholinergics or tiapride as a co-medication against EPS compared to 28.5% and 8.9% of patients treated with other first- ($p<.0001$) and second-generation antipsychotics ($p<.0001$), respectively. Thus, second-generation antipsychotics show a clear advantage over flupentixol concerning EPS co-medication, while flupentixol showed a clear over other first-generation antipsychotics (see Table 3 and Fig. 4).

Regarding prescriptions of sedative drugs, patients treated with flupentixol (predicted probability of having prescription for sedative drugs, 12.9%) had about the same amount of prescriptions compared to other first- (predicted probability, 13.6%; $p=0.2037$) and second-generation antipsychotic drugs (predicted probability, 11.3%; $p=0.6793$). Compared to patients treated with flupentixol, predicted probability of having a prescription for anxiolytic drugs did not differ significantly for patients treated with other first-generation antipsychotics (flupentixol, 16.2% vs. other first-generation antipsychotics, 17.7%; $p=0.4384$) and for patients treated with second-generation antipsychotics (flupentixol, 16.2% vs. second-generation antipsychotics, 17.2%; $p=0.5434$) (see Fig. 4).

Sensitivity analysis

Except for the model on prescriptions for anticholinergics or tiapride as a co-medication against EPS, none of the

Table 2 Characteristics of study population by medication subgroup

	Flupentixol	All other first-generation antipsychotics	Second generation antipsychotics (non-switchers)
Number of patients	177	429	2,284
Age [SD]	42.6 [12.9]	45.8 [13.4]	39.2 [14.2]
Gender (% female)	49.2%	45.2%	44.8%
Severity (i.e. prior hospitalisation)	27.6 [42.4]	20.1 [33.5]	22.8 [38.5]

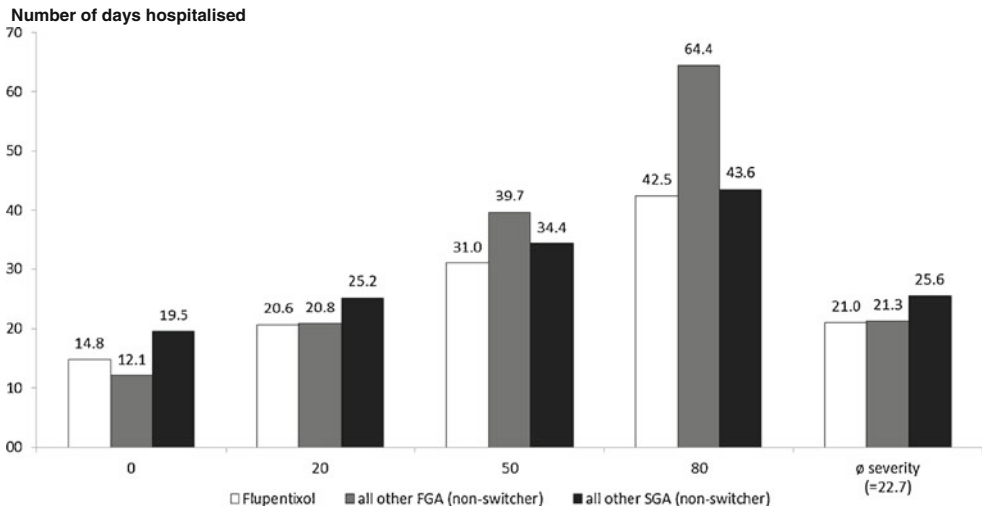

Fig. 2 Predicted hospitalisation in days during follow-up, depending on severity (age=40.4 years, male). Severity is the average number of days previously hospitalised per year. *FGA* first-generation antipsychotics, *SGA* second-generation antipsychotics

specifications of depot use reached significance ($p<0.0500$) in any regression model. In none of the models, the inclusion of the variable had a considerable impact on the comparisons between flupentixol and first- or second-generation antipsychotics. Differentiating between clozapine and other second-generation antipsychotics, the predicted probability of having a prescription for drugs against EPS was 4.0% for clozapine. This increased the predicted probability of having a prescription for drugs against EPS for all other SGAs to 10.1%. However, the difference to flupentixol remained significant in both comparisons. Regarding prescriptions for sedative drugs, clozapine had a predicted probability of having a prescription of 5.2%, significantly lower compared to flupentixol ($p=0.0003$), while the predicted probability of having a prescription for sedative drugs for all other SGAs slightly increased to 12.9% and remained not significantly different compared to flupentixol. Regarding prescriptions for anxiolytics, the predicted probability were 20.0% and 16.3% for clozapine and all other SGAs, respectively. Differences compared to flupentixol remained insignificant. In the cost model (predicted average cost: clozapine 6,731 €, all other SGAs 6,475 €, flupentixol 4,846 €) and in the models for bed days, significance of results did not changed as well.

Discussion

In this 'real world' retrospective cohort study of patients with schizophrenia, the effectiveness of flupentixol on rehospitalisation measures (mean days hospitalised) was similar to that of second-generation antipsychotics. These findings are, on one hand, in line with an earlier study (Stargardt et al. 2008). Also, in a randomised double-blind study with 153 chronic schizophrenic patients, flupentixol was shown not to be inferior to risperidone regarding the control of negative schizophrenic symptoms. General psychopathology and positive schizophrenic symptoms were also improved compared to risperidone, and there was a trend in favour of flupentixol concerning the improvement of depressive symptoms (Philipp et al. 2003).

Furthermore, Gattaz et al. (2004) compared the efficacy and safety of flupentixol versus olanzapine in a double-blind, 4-week study with 28 schizophrenic inpatients. There

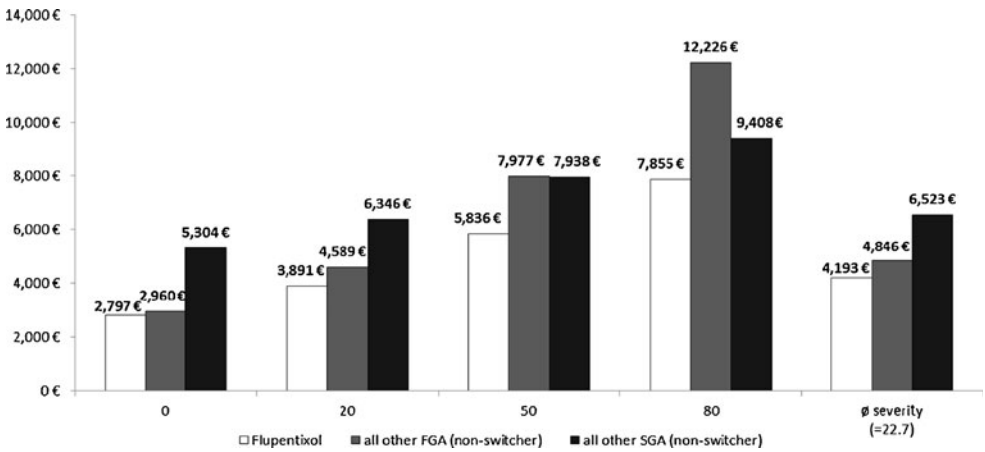

Fig. 3 Predicted cost during follow-up depending on severity (age=40.4 years, male). Severity is the average number of days previously hospitalised per year. *FGA* first-generation antipsychotics, *SGA* second-generation antipsychotics

Table 3 Results from regression models

Depending	Hospital days		Costs	Prescription for anticholinergic drugs	Prescription for sedative drugs	Prescription for anxiolytic drugs
Model	Inflation part of the model	Poisson regression	Gamma	Logit	Logit	Logit
Intercept	0.3167	3.9328***	8.2283***	−1.3395***	−1.8558***	−1.6093***
Gender	−0.0982		0.0794*	−0.0532	−0.1028	−0.0667
Age	0.0163***	−0.0095***	−0.0094***	0.0013	0.0086	0.0212*
Age^2	−0.0001	0.0002***	0.0002*	−0.0001	−0.0009	−0.0006
Severity	−0.0155***	0.0061***	0.01498***	0.0028	0.0017	0.0061*
Severity^2	0.00004***	−0.00001***	−0.0001*			−0.00003
Medication						
Second-generation antipsychotics (non-switcher)	0.0349	0.2102***	0.4704***	−0.9652***	−0.1576	0.0696
Flupentixol (non-switcher)			Reference group			
All other first-generation antipsychotics (non-switcher)	0.1598	0.1263***	0.1791	0.4440***	0.0610	0.1057
Interactions						
Age×medication				Included	Included	Included
Age^2×medication				Included	Included	Included
Severity×medication	Included	Included	Included	Included		Included
Severity^2×medication			Included			

*$p<0.05$; **$p<0.01$; ***$p<0.001$

were no significant differences between the groups concerning the improvement of negative symptoms and general psychopathology. Subjective quality of life, as an important factor for compliance in chronic schizophrenic patients, was investigated in a multi-centre, double-blind trial with 76 patients treated with flupentixol and 77 patients treated with risperidone (Hertling et al. 2003). Both groups showed a significant improvement regarding subjective quality of life. In the flupentixol group, the 'ability to cope with stress', 'feel more relaxed' and the 'ability to achieve something' improved significantly more than in the risperidone group. Evidence also suggested that flupentixol is effective in treating negative symptoms (Pach et al. 1998a; Philipp et al. 2003; Gattaz et al. 2004) and useful as an antidepressant (Gruber and Cole 1991; Budde 1992). These effects are probably based on the different receptor profile of flupentixol compared to other first-generation antipsychotics such as haloperidol. Flupentixol shows similarities to some second-generation antipsychotics, mainly the blockage of D2- and 5-HTA2 receptors (Möller 1999; Kühn et al. 2000).

On the other hand, the number of patients treated exclusively with flupentixol was rather low in our sample (177 patients, 6.1% of the study population). As the Poisson regression model for length of stay if hospitalised is only based on the 70 patients treated with flupentixol who were hospitalised during follow-up, the results from the Poisson regression model may be extrapolating out of the data range. Also, as the study used administrative data from four sickness funds, the study population may not be entirely representative of the wider population. However, one of the sickness funds operates nationwide (Techniker Krankenkasse) while the three large regional sickness funds (AOK) cover three major regions in Germany.

Although rehospitalisation might be the most important outcome parameter from an economic perspective (Almond et al. 2004), second-generation antipsychotics might still be the preferred treatment option because of the more favourable side-effect profile. The results in our study on disease- or medication-related effects under flupentixol treatment, i.e. co-medication against EPS, are consistent with the international literature (Tollefson et al. 1997; Csernansky et al. 2002; Gattaz et al. 2004; Weinbrenner et al. 2008).

In contrast to randomised clinical trials or prospective observational studies, neither data from clinical severity assessments nor information on other factors known to influence the risk of relapse such as engagement in community services, living conditions or family background were available in our study (Kilian et al. 2004; Lyons et al. 1997). Utilisation of outpatient care or non-physician care, e.g. psychoeducation, could not be examined. Therefore, our cost data only give a limited

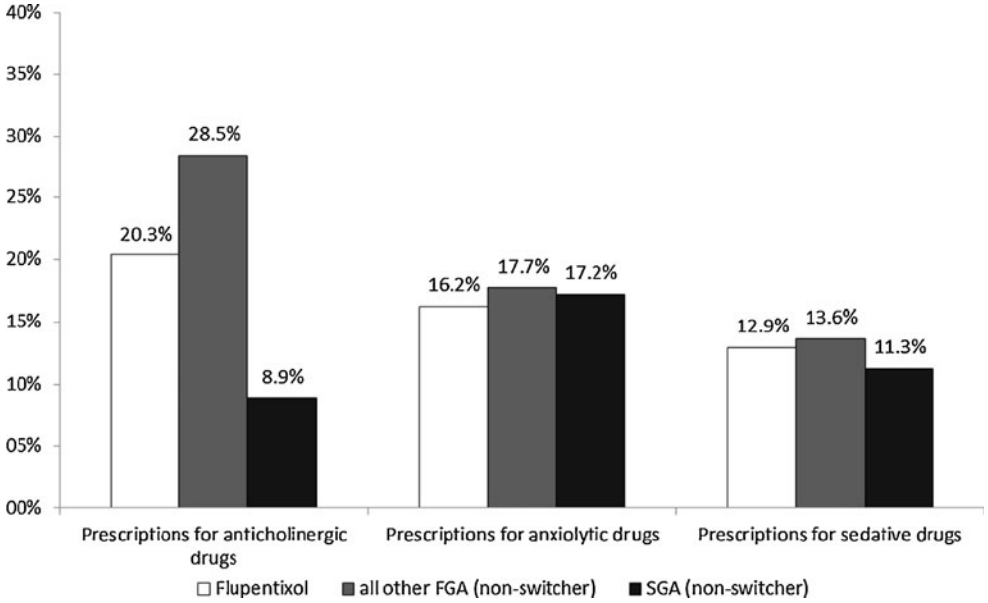

Fig. 4 Predicted probability of receiving co-medication by drug treatment (age=40.4 years, male). *FGA* first-generation antipsychotics, *SGA* second-generation antipsychotics

perspective on direct medical costs. For Germany, a systematic review on the cost of schizophrenia in 2009 concluded that annual direct medical cost inflation in 2007 was between 14,000 € and 18,000 €. In studies calculating cost per patient, the combined cost of inpatient and pharmaceutical treatment amounted to between 26% and 80% of total treatment cost depending on the recruitment setting (Konnopka et al. 2009). Using the top-down approach, the federal statistical office amounted 78% of direct medical cost to inpatient and pharmaceutical treatment (Konnopka et al. 2009).

In addition, the percentage of switchers among patients treated with first-generation antipsychotics was larger than the percentage of switchers among second-generation antipsychotics. This might bias results. Furthermore, it is well-known that psychopathology or hospital readmission rates only partially reflect general outcome. Quality of life, psychosocial re-integration and the occupational situation are other important factors to measure effectiveness.

Available data also did not allow us to differentiate to what extent hospital readmissions were due to loss of medication response or to non-compliance. According to Weiden and Olfson (1995), the loss of efficacy of antipsychotics after 1 year is caused by loss of medication response in 68% and due to non-compliance in 32% of cases. Second-generation antipsychotics seem to achieve higher compliance rates than first-generation antipsychotics (Zhang et al. 2004; Thieda et al. 2003; Wahlbeck et al. 1999). However, we could not assess to what extent wrong dosage strength or non-compliance contributed to hospital readmission in our study.

As several studies suggest that depot medication with flupentixol might have a positive effect on the long-term course of patients with schizophrenia (Knudsen 1985; Eberhard and Hellbom 1986; Pach et al. 1998b), this may bias our results. In our study, the percentage of patients who had received at least one antipsychotic depot medication was substantially higher for flupentixol (10.1% of subgroup) and other first-generation antipsychotics (8.2% of subgroup) than for the second-generation antipsychotics (1.5% of subgroup). However, as our sensitivity analyses show, the inclusion of a variable indicating depot use had—probably due to the low number of patients or their heterogeneity—no effect on outcomes.

Another limitation is that first- and second-generation antipsychotics were considered as a homogenous group of drugs. In reality, there are differences in the efficacy and particularly in the side-effect profile between individual drugs. When differentiating between clozapine and all other second-generation antipsychotics, there was a change in comparisons with flupentixol regarding prescriptions for sedative drugs. However, differentiating between clozapine and SGAs did result in major changes of results. In addition, prior hospitalisation is only one measure for the severity of schizophrenia, and it is unknown to what extent it corresponds to psychopathological rating scales used to determine severity in the clinical setting. Prior hospitalisation itself may have been influenced by the type of neuroleptic treatment or switching behaviour during the previous three or more years.

Finally, it has to be mentioned that our data provide no information why one patient was treated by a first-generation antipsychotic and the other one by a second-generation antipsychotic. Clinical decision to the individual patient disease history or degree of his illness is naturally not reflected within data from health insurances. This is, of course, a limitation, which can be only solved by a prospective study including data from hospitals and psychiatrists in practice.

Conclusions

In summary, from a clinical perspective, the similarity in a number of effectiveness measures between flupentixol and second-generation antipsychotics in routine care is the most interesting finding of our study. This is in line with findings from clinical trials where flupentixol was valued as a 'partial second-generation antipsychotic drug'. The increased costs of second-generation antipsychotics were not balanced by cost savings from shorter inpatient stays in our study. Thus, flupentixol might be an attractive alternative in terms of costs and effectiveness in the long-term treatment of patients with schizophrenia.

Acknowledgements This study was kindly supported by an investigator-initiated trial grant from Bayer Vital GmbH. We are very grateful to the Techniker Krankenkasse, AOK Berlin, AOK Baden-Wuerttemberg and AOK Westfalen-Lippe for their kind support in granting access to the sickness fund databases and for their help with data extraction.

References

Almond S, Knapp M, Francois C et al (2004) Relapse in schizophrenia: costs, clinical outcomes and quality of life. Br J Psychiatry 184:346–351

Budde G (1992) Efficacy and tolerability of flupenthixol decanoate in the treatment of depression and psychosomatic disorders: a multicenter trial in general practice. Prog Neuropsychopharmacol Biol Psychiatr 16:677–689

Conley RR, Love RC, Kelly DL et al (1999) Rehospitalisation rates of patients recently discharged on a regimen of risperidone or clozapine. Am J Psychiatry 156:863–868

Conley RR, Kelly DL, Love RC et al (2003) Rehospitalization risk with second-generation and depot antipsychotics. Ann Clin Psychiatry 15:23–31

Crossley NA, Constante M, McGuire P, Power P (2010) Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. Br J Psychiatry 196:434–439

Csernansky JG, Mahmoud R, Brenner R (2002) A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 346:16–22

Davis J, Chen N, Glick I (2003) A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 60:553–564

Eberhard G, Hellbom E (1986) Haloperidol decanoate and flupentixol decanoate in schizophrenia. A long-term double-blind cross-over comparison. Acta Psychiatr Scand 74:255–262

Gattaz WF, Diehl A, Geuppert MS et al (2004) Olanzapine versus flupentixol in the treatment of inpatients with schizophrenia: a randomized double-blind trial. Pharmacopsychiatry 37:279–285

Geddes J, Freemantle N, Harrison P et al (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 321:1371–1376

Gruber AJ, Cole JO (1991) Antidepressant effects of flupenthixol. Pharmacotherapy 11:450–459

Haro JM, Edgell ET, Frewer P et al (2003) The European schizophrenia outpatient health outcomes (SOHO) study: baseline findings across country and treatment. Acta Psychiatr Scand 107:7–15

Hertling I, Philipp M, Dvorak A et al (2003) Flupentixol versus risperidone: subjective quality of life as an important factor for compliance in chronic schizophrenic patients. Neuropsychobiology 47:37–46

Jones PB, Barnes TR, Davies L et al (2006) Randomized controlled trial of the effect on quality of life of second- vs. first-generation antipsychotic drugs in schizophrenia: cost utility of the latest antipsychotic drugs in schizophrenia study (CUtLASS 1). Arch Gen Psychiatry 63:1079–1087

Kilian R, Angermeyer MC, Becker T (2004) Methodische Grundlagen naturalistischer Beobachtungsstudien zur ökonomischen evaluation der Neuroleptikabehandlung bei schizophrenen Erkrankungen. Gesundheitswesen 66:180–185

Kissling W, Höffler J, Seemann U et al (1999) Direct and indirect costs of schizophrenia. Fortschr Neurol Psychiatr 67:29–36

Knudsen P (1985) Chemotherapy with neuroleptics. Clinical and pharmacokinetic aspects with a particular view to depot preparations. Acta Psychiatr Scand 322:51–75

Konnopka A, Klingberg S, Wittorf A, König HH (2009) The cost of schizophrenia in Germany: a systematic review of the literature. Psychiat Prax 36:211–218

Kühn KU, Meyer K, Maier W (2000) Flupentixol-a partial atypical neuroleptic. Fortschr Neurol Psychiatr 68:38–41

Lieberman JA, Stroup TS, McEvoy JP et al (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223

Lyons JS, O'Mahoney MT, Miller SI et al (1997) Predicting readmission to the psychiatric hospital in a managed care environment: implications for quality indicators. Am J Psychiatry 154:337–340

Möller HJ (1999) Atypical neuroleptics: a new approach in the treatment of negative symptoms. Eur Arch Psychiatr Clin Neurol sci 24:99–107

Müller P, Nerenz H, Schaefer E (2002) The risk of rehospitalisation during therapy with atypical and typical neuroleptics—a contribution to differential indication. Psychiatr Prax 29:388–391

Pach J, Bertling R, Finkbeiner T et al (1998a) Rezidive bei schizophrenen Erkrankungen unter Depot-Neuroleptika. Ergebnisse einer 1-jährigen Doppelblindstudie mit Flupentixol-Decanoat. Psychopharmakotherapie 5:161–165

Pach J, Finkbeiner T, Glaser T et al (1998b) Positiv- und Negativsymptomatik bei chronisch schizophrenen Patienten unter Erhaltungstherapie mit Flupentixoldecanoat im 12-Monatsverlauf. Fortschr Neurol Psychiatr 66:442–449

Philipp M, Lesch OM, Schmauss M et al (2003) Comparative effectiveness of flupentixol and risperidone on negative symptoms of schizophrenia. Psychiatr Prax 30:94–96

Rosenheck R, Perlick D, Bingham S et al (2003) Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA 290:2693–2702

Saha S, Chant D, Welham J, McGrath J (2005) A systematic review of the prevalence of schizophrenia. PLoS Med 2:e141

Sernyak MJ, Leslie D, Rosenheck R (2003) Use of system-wide outcomes monitoring data to compare the effectiveness of atypical neuroleptic medications. Am J Psychiatry 160:310–315

Stargardt T, Weinbrenner S, Busse R et al (2008) Effectiveness and cost of atypical versus typical antipsychotic treatment for schizophrenia in routine care. J Ment Health Policy Econ 11:89–97

Thieda P, Beard S, Richter A et al (2003) An economic review of compliance with medication therapy in the treatment of schizophrenia. Psychiatr Serv 54:508–516

Tiihonen J, Wahlbeck K, Lönnqvist J et al (2006) Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia

and schizoaffective disorder: observational follow-up study. BMJ 333:224

Tollefson GD, Beasley CM, Tran PV et al (1997) Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 154:457–465

Wahlbeck K, Cheine M, Essali A et al (1999) Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 156:990–999

Weiden PJ, Olfson M (1995) Cost of relapse in schizophrenia. Schizophr Bull 21:419–429

Weinbrenner S, Assion HJ, Stargardt T et al (2008) Drug prescription patterns in schizophrenia outpatients: analysis of data from German health insurance fund. Pharmacopsychiatry 41:1–6

Zhang PL, Santos JM, Newcomer J et al (2004) Impact of atypical antipsychotics on quality of life, selfreport of symptom severity, and demand of services in chronically psychotic patients. Schizophr Res 71:137–144