Peer reviewed article

# Antipsychotic use in patients with schizophrenia treated in private psychiatry

*Andor E. Simon*[a], *Manuela Peter*[b], *Lorenzo Hess*[b], *Claude Valterio*[c]

[a] Spezialsprechstunde zur Abklärung und Behandlung psychotischer Frühphasen, Externe Psychiatrische Dienste Baselland, Bruderholz, Switzerland
[b] Brunner & Hess Software AG, Zürich, Switzerland
[c] Sanofi-Synthélabo Switzerland, Meyrin/Geneva, Switzerland

## Summary

*Questions under study:* The aim of this study was to assess antipsychotic treatment practices among private psychiatrists in Switzerland.

*Methods:* For each patient seen during 4 consecutive weeks, 101 participating private psychiatrists documented psychiatric diagnosis. For each schizophrenic patient, demographic details as well as treatment issues were assessed in a questionnaire-based survey. Participating psychiatrists were representative for Swiss private psychiatry with regards to gender distribution and region of practice.

*Results:* Overall, 8425 patients were assessed in our survey. Of these, 905 patients (10.7%) received a diagnosis of schizophrenic psychoses, of whom 733 details on antipsychotic treatment were documented. 73.1% of these patients received second-generation antipsychotics. Most private psychiatrists prescribed antipsychotic monotherapy and maintained antipsychotic treatment according to recommendation from international guidelines. Almost half of these patients had a history of medication non-adherence, with non-compliance being the most frequent reason.

*Conclusion:* The findings of this survey suggest that Swiss private psychiatrists prescribe according to international guidelines in terms of drug choice as well as maintenance treatment. Moreover they show low rates of polypharmacy and comedication practice as compared to their colleagues in other European countries. This may reflect solid experience in prescribing second-generation antipsychotics of a subgroup of private psychiatrists in Switzerland.

*Key words: schizophrenia; private practice; antipsychotics; polypharmacy; comedication; non-compliance; non-adherence*

## Introduction

Treatment of schizophrenia underwent a dramatic breakthrough with the introduction of the first antipsychotic in the mid-fifties and the group of first-generation antipsychotics (FGA) in the following years [1]. A further milestone was the development of the first atypical or second-generation antipsychotic (SGA), clozapine, in 1969 which today is still considered the treatment of choice for treatment resistant patients with schizophrenia [2]. Over the last years, the emergence of a number of other SGAs have led to a shift in the pharmacological treatment of schizophrenia, with use of SGAs in general favoured over the use of FGAs. The pharmacological treatment of schizophrenia has been thoroughly evaluated and standardised in guidelines (eg "The Expert Consensus Guidelines Series") [3]. Recent meta-analyses suggested that some SGAs have higher efficacy than FGAs, concluding that SGAs as a group were heterogeneous in terms of efficacy [4, 5], and that SGAs have the potential to reduce relapse rates [6]. It is commonly acknowledged today that patients with multiple episodes of schizophrenia must adhere to antipsychotic treatment for at least 5 years, and that after a first episode, maintenance treatment of at least 1 to 2 years of duration must be established [3].

Against the background of the recommended use of SGAs in schizophrenic patients, a growing body of literature has elucidated a number of issues related to SGAs, such as frequency of prescription, combination therapy, side effects and their potential influence on patient compliance. With regard to the prescription prevalence of SGAs as compared to FGAs, between-country comparisons revealed heterogeneous practices [7, 8]. Other studies found high rates of combination therapy with SGAs, either with FGAs, other SGAs, or with SSRIs [8, 9]. Although being embraced as an increasingly common practice by physicians in the treatment of schizophrenia, there is a lack of

This study was supported by an unrestricted grant from Sanofi-Synthélabo SA, Switzerland.

data documenting this trend or supporting its effectiveness [10]. The lack of evidence base for combination therapy requests attention in view of the relative high costs of SGAs [9]. Furthermore, it should be considered that combining several antipsychotics increases the risk of side-effects and mortality [11] and jeopardizes the existing therapy advantages of the SGAs [10].

A major problem in the pharmacological treatment of schizophrenic patients is their often reduced compliance with antipsychotic medication [12]. Treatment discontinuity negatively affects patients' treatment outcome [13] and may lead to waste of therapeutic resources. A prerequisite for good treatment outcome, therefore, is treatment continuity [14]. However, premature treatment termination is relatively frequent, with estimates among psychotic patients ranging from 24 to 90% [15]. Patient-related factors associated with non-compliance in psychosis are young age and male gender, negative attitudes towards medication, reduced awareness of either illness or medication effects, delusional symptoms, substance abuse, unemployment and low social functioning [15–17]. However, one of the most important factors for non-compliance, side effects, is treatment-related [18, 19]. Compared to FGAs, SGAs showed a reduced propensity to produce extra-pyramidal symptoms [20] and tardive dyskinesia [21], contributing to the superiority of SGAs over FGAs with regard to medication adherence [22, 23]. However, sedation and weight gain may be a common problem with atypical antipsychotic treatment [24]. Furthermore, metabolic disorders such as hyperglycemia or diabetes mellitus have been reported in patients treated with atypical antipsychotics [25].

The aim of this study was to explore whether recommendations from international guidelines [3] regarding the use of SGAs *vs* FGAs for the treatment of schizophrenic patients were applied in private psychiatry in Switzerland. Together with out-patient services and general practitioners, private psychiatrists constitute a cornerstone in the community health care of these patients. Better knowledge on issues of treatment strategies are warranted, as it may allow more focussed education for private psychiatrists and further appropriate treatment of non-institutionalised patients suffering from schizophrenia.

## Materials and methods

### Participants

As of January 2003, 1516 psychiatrists were working in private practice in Switzerland (men: n = 990, 65%; women: n = 526, 35%). Of these, 982 (65%) were working in the German speaking part of the country, 476 (32%) in the French speaking part of the country, and 48 (3%) in the Italian speaking part of the country.

After stratification according to the linguistic distribution in Switzerland, 104 private psychiatrists were individually visited by representatives (of Sanofi-Synthélabo) between January and June 2003 and enrolled in the survey. They were provided a questionnaire and asked to document all patients that they saw for the duration of four consecutive weeks. For patients with more than one contact during that period, only one contact was considered. One participating psychiatrist was excluded from final analysis due to a documentation solely based on schizophrenic patients, and two participants were excluded due to their specialisation in child psychiatry.

### Questionnaire

The questionnaire listed six major psychiatric disorders (mood and anxiety disorders, substance use disorders, personality disorders, affective psychoses and schizophrenia). The participants were asked to indicate the diagnoses, age and gender of each patient. For patients with schizophrenia, the participants had to answer further questions, listed in an additional form, that covered the following aspects: duration of illness since first episode; type of medication; duration of antipsychotic maintenance treatment; and treatment compliance of patients. The participants also had to give information on patient referral source and treatment setting (eg treatment in collaboration with a GP, or psychiatric out-patient service, or alone). However, these data are not subject of this paper. All data on patients remained anonymous throughout the survey.

### Statistical analyses

Logistic regression was used to identify predictive factors for several dependent variables. The estimation was carried out with a backward stepwise method (likelihood ratio). A P-value of $<0.05$ was considered to indicate statistical significance. The statistical analysis was calculated with SPSS for Windows (Version 11.5).

## Results

### Characteristics of private psychiatrists

101 private psychiatrists (male: n = 73, 72.3%; female: n = 28, 27.7%) participated in the survey. 98 psychiatrists participated during 4 weeks, 2 during 3 weeks, 1 during 2 weeks. 62 were from the German speaking, 29 from the French speaking, and 10 from the Italian speaking part of Switzerland. 79 (78.2%) worked in urban, 19 (18.8%) in semi-urban, and 3 (3.0%) in rural regions. The participating sample was representative of the whole sample of Swiss psychiatrists in terms of gender distribution and region of practice. Mean duration since graduating from medical school was 19.6 years (SD ± 7.8).

### Patient characteristics

Of the 8425 patients included in the survey, 905 (10.7%) had a diagnosis of schizophrenia. For 733 (81%) of the 905 patients included with schizophrenic psychosis, additional information was provided by the participating private psychiatrists. Male outweighed female patients (53.1% vs 45.0%). 17.1% of the patients were below 30 years of age, 55.6% between 30 and 49 years of age, and 27.3% were older than or equal to 50 years. Overall, the majority of schizophrenic patients (n = 621; 84.7%) had an illness duration of over 2 years, and in only a few patients a beginning psychosis was suspected (n = 13; 1.8%). Schizophrenic disorders yielded a relatively low comorbidity rate with other disorders (35.6%).

### Antipsychotic treatment of patients with schizophrenia

Of the 733 patients with schizophrenia for whom additional information was available, 685 (93.5%) were prescribed antipsychotic medication by their treating private psychiatrists, 13 patients (1.8%) received other than antipsychotic medication, whereas 35 patients (4.8%) received no medication at all. Of the 685 patients with antipsychotic treatment, 536 (78.2%) were prescribed SGAs and 215 (31.4%) FGAs. Antidepressants were prescribed in 152 (22.2%) of these patients, mood stabilizers in 75 (10.9%), and tranquilizers in 134 patients (19.6%). Patterns of antipsychotic prescription (FGAs vs SGAs) did not differ between male or female psychiatrists (FGAs: 34.6% vs 30.2%; SGAs: 79.4% vs 75.4%) and was independent of their years since graduating from medical school (FGAs: 28.4% (<20 y) vs 33.1% (≥20 y); SGAs: 81.1% vs 76.6%). Psychiatrists in urban regions prescribed slightly more often SGAs than psychiatrists in rural regions (79.7% vs 73.8%).

There was no difference between male and female patients in receiving SGAs (77.9% vs 78.0%). There was an inverse pattern in the antipsychotic use (FGAs vs SGAs) across age groups. The patients younger than 30 years of age received FGAs in 13.6% and SGAs in 92.7% of the cases, whereas of the patients above 60 years of age, 51.9% of the cases received FGAs and 51.9% SGAs. Patients with an illness duration of less than 2 years were prescribed FGAs in 14.9% and SGAs in 94.7% of the cases, whereas for patients with an illness duration of above 2 years, FGAs were used in 34.0% and SGAs in 75.6% of the cases.

### Combination therapy of antipsychotics

Tables 1 to 4 show combination therapy of antipsychotics. Within combination therapy, we defined comedication as a prescription of another drug in addition to an antipsychotic within the survey interval of 4 weeks, whereas polypharmacy was defined as the prescription of more than one antipsychotic prescribed concurrently within the assessed survey interval of 4 weeks. Table 1 shows how often one particular medication of a medication class was prescribed alone or as comedication. SGAs were more often prescribed alone compared to FGAs (48.1% vs 37.2%). As a group, however, there was no difference between SGAs and FGAs (56.9% vs 54.4%) in terms of comedication (see table 2). Table 3 shows that SGAs were prescribed as monotherapy in 84.6% and FGAs in 68.4% of the cases. Table 4 illustrates details of the cases in which polypharmacy was indicated. A logistic regression with comedication as the dependent variable showed that neither gender, illness duration,

**Table 1**
Comedication (number of medications).

| Medication | one | two | three or more |
|---|---|---|---|
| Typical Antipsychotics (n = 215) | 37.2% | 31.6% | 31.2% |
| Atypical Antipsychotics (n = 536) | 48.1% | 30.8% | 21.1% |
| Antidepressiva (n = 156) | 0.6% | 39.1% | 60.3% |
| Mood-Stabilizers (n = 81) | 4.9% | 46.9% | 48.1% |
| Tranquilizers / Sedativa / Hypnotica (n = 140) | 1.4% | 35.0% | 63.6% |

**Table 2**
Comedication (number of medications of other classes).

| Medication | none | one | two or more |
|---|---|---|---|
| Typical antipsychotics (n = 215) | 54.4% | 32.1% | 13.5% |
| Atypical antipsychotics (n = 536) | 56.9% | 29.7% | 13.4% |
| Antidepressiva (n = 156) | 0.6% | 50.0% | 49.4% |
| Mood-stabilizers (n = 81) | 6.2% | 60.5% | 33.3% |
| Tranquilizers / sedativa / hypnotica (n = 140) | 1.4% | 47.1% | 51.4% |

**Table 3**
Polypharmacy (only for no comedication).

| Medication | monopharmacy | polypharmacy |
|---|---|---|
| Typical Antipsychotics (n = 117) | 68.4% | 31.6% |
| Atypical Antipsychotics (n = 305) | 84.6% | 15.4% |

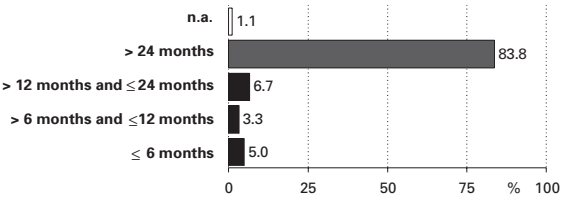
**Table 4**
Polypharmacy: Combination with 1 other medication.

| Medication | In combination with | |
|---|---|---|
| | typical antipsychotics | atypical antipsychotics |
| Typical Antipsychotics (n = 34) | 23.5% | 76.5% |
| Atypical Antipsychotics (n = 44) | 59.1% | 40.9% |

**Table 5**
Withdrawal of medication (n = 685).

| Withdrawal | |
|---|---|
| Yes | 44.8% |
| No | 55.0% |
| n.a. | 0.1% |
| **Reason of Withdrawal (n = 307)** | |
| Adverse Events | 36.2% |
| Insufficient Efficacy | 9.1% |
| Insufficient Compliance | 77.2% |
| Others | 8.1% |

**Figure 1**
Intended duration of medication in 698 patients with schizophrenic psychoses.




the combination of illness duration and age, nor the combination of comorbidity and gender were related to a treatment with other medication in addition to an antipsychotic. A significant effect, however, was seen with the combination of comorbidity and age ($p < 0.001$), where older patients with a comorbidity more often had comedication. Taken together, only 10.4% of the variance could be explained by this model (Nagelkerke $R^2$).

Further logistic regression analysis searched to explain the influence of the above mentioned variables on polypharmacy. No variable remained in the model, thus, neither gender, age, illness duration nor comorbidity were related to the prescription of more than one antipsychotic.

## Intended duration of antipsychotic maintenance treatment

Figure 1 shows that the vast majority of private psychiatrists (83.8%) intend to prescribe antipsychotic maintenance treatment for a period of at least 2 years. A logistic regression revealed that variables pertaining to private psychiatrists, such as years since graduating from medical school (<20y/ ≥20 y), gender, number of schizophrenic patients treated during the survey interval (1–5/>5), as well as region of practice were not related to intended duration of maintenance treatment. Similarly, with regard to variables pertaining to schizophrenic patients, gender did not significantly influence the intended duration of antipsychotic treatment. However, age showed a significant effect, with shorter maintenance treatment being intended for younger patients ($p = 0.01$, OR: 1.03; 95% CI: [1.01, 1.05]). Whereas for patients with an illness duration of less than 2 years the intended duration of maintenance treatment was less than 2 years in 48.9% and more than 2 years in 46.8% of all cases, a vast majority of psychiatrists (91.2%) favoured a maintenance treatment of more than 2 years in patients with illness durations of over 2 years ($p < 0.001$, OR: 9.31, 95%CI: [5.45, 15.93]). The variables included in this regression equation were, however, only able to account for 23.1% of the variance (Nagelkerke $R^2$).

## Compliance of schizophrenic patients with antipsychotic treatment

Table 5 shows the frequency and reasons of medication withdrawal. A substantial number of patients (n = 307; 44.8%) had a history of medication non-adherence, and among these, non-compliance was a major motive (77.2%). A logistic regression model showed that history of medication non-adherence was unrelated to illness duration, but to female gender ($p = 0.037$, OR: 1.42, 95% CI: [1.02, 1.97]) as well as to patients with more than 2 visits during the survey interval of 4 weeks ($p = 0.01$, OR: 2.49, 95% CI: [1.25, 4.96]). Age was slightly negatively correlated with medication non-adherence ($p = 0.001$, OR: 0.98, 95% CI: [0.97, 0.99]), but had a significant interaction with substance use comorbidity ($p = 0.011$) and should therefore be interpreted carefully.

History of medication non-adherence was similar in patients on FGAs (40.5%) and patients on SGAs (47.0%) as well as in patients on comedication (41.4%) and without comedication (47.3%), and each variable was not relevant for the explanation of medication non-adherence in the model. A slight difference was observed between patients with polypharmacy (56.4%) and patients with monopharmacy (45.9%). This variable was not included into the model because it represented only a part of the patients. 29.9% of the patients treated with FGAs and 38.9% of the patients treated with SGAs indicated an adverse event as reason for medication non-adherence. Adverse events occurred in 39.8% of the patients with no comedication and in 30.6% with comedication, and in 40.0% with monopharmacy and in 38.7% with polypharmacy. However, the questionnaire was not designed to assess type of adverse event. It is noteworthy that the variables included into the regression model were only able to explain 5.6% of the variance (Nagelkerke $R^2$).

## Discussion

### Limitations

This study was designed to investigate trends of antipsychotic treatment strategies in private practice in Switzerland. Before interpreting the results, a number of limitations need to be forwarded. First, the number of private psychiatrists who participated in our survey made up only 6.3% of all psychiatrists in private practice in Switzerland. We have to assume that this study, like any such survey, is limited by the tendency to include cooperative respondents. Furthermore, given the strong psychoanalytical tradition in Swiss private psychiatry, the investigated sample may be biased towards psychiatrists who are more interested in pharmacological and biological aspects of psychiatry, in particular psychosis. Also, no information was recorded about refusal rate of psychiatrists to participate in this survey.

Second, even if the applied questionnaire consisted of items that mostly assessed anamnestic and diagnostic information, the question about intended duration of maintenance treatment may not reflect the "real world" situation for each patient and thus not assess actual behaviour, but be considered more of a "proxy" measure of intended behaviour [26]. Additionally, our survey was not able to control for the correctness of patient diagnoses indicated by private psychiatrists. Third, mail surveys are considered to be inferior in terms of cooperation, interview administration (eg, rapport and confidence), confidentiality, and social desirability compared to telephone or personal interviewing [27]. Fourth, the training of psychiatrists may vary across countries; thus, the findings of our study may not apply to other settings. Fifth, the regression equation models accounted for 6 to 23% of the variance, suggesting that our questionnaire did not address other variables possibly influencing treatment choice, maintenance treatment and treatment compliance. Finally, given the sparse literature on characteristics of schizophrenic patients treated in private psychiatry [28, 29], it remains unclear whether the recruited patient sample was representative of the overall sample of schizophrenic patients treated in private psychiatry in Switzerland.

Nevertheless, some strengths of this survey should be mentioned: this survey includes a representative sample of Swiss private psychiatrists in terms of gender and geographic coverage, thus allowing to draw a valid picture of their treatment strategies regarding schizophrenic patients in Switzerland. Moreover, the 4-week survey duration enabled us to capture a substantial number of patients, including patients suffering from schizophrenia. To the best of our knowledge, this is the first survey in Switzerland to comprehensively assess treatment strategies of private psychiatrists with regard to schizophrenic patients.

### Type of antipsychotic treatment

One of the most significant findings of our survey was the high prescription rate of SGAs (78.2%) among patients receiving antipsychotic treatment. These prescription practices were independent of the assessed socio-demographic variables of the psychiatrists. However, the fraction of FGAs increased for older patients with longer durations of illness as opposed to SGAs, which may reflect that some patients were started on FGAs before the emergence of SGAs (except clozapine) and never were switched to newer antipsychotics. Our finding of a high prescription rate of SGAs suggests that at least a part of private psychiatrists in Switzerland follow the recommendations of current treatment guidelines [3]. Furthermore, it suggests that the Swiss prescription practices may correspond more to pharmaco-epidemiological data from the U.S., where SGAs rates of 40 to 70% in out-patient care were reported [9, 30], than to data from other European countries [31, 32]. For example, in a German naturalistic study of 725 inpatients with ICD-10 diagnoses F 20, 22–25, SGAs were prescribed as first choice drugs only in 15%. Further, it has been reported that of all prescribed antipsychotics in German out-patient health care, 23% are SGAs [31]. In a sample of British patients with schizophrenia, 26% were treated with SGAs [32]. Common to all SGAs are significantly higher acquisition costs in comparison with FGAs. Even though the acquisition costs of the drugs represents only a very small contribution to the total costs arising in the treatment of schizophrenia [33], it may be in this field that attempts are being made on the part of the health authorities to limit the costs. Whilst this may influence prescribing practices of private psychiatrists, this may not substantially apply to Switzerland, where private insurance companies cover the costs for antipsychotic treatment

Against the background of the high costs of SGAs, the finding that a vast majority of private psychiatrists in our survey follow antipsychotic monotherapy, is noteworthy when comparing with reported data from other countries, where polypharmacy was suggested to be the rule rather than the exception [8]. In a U.S. study of 836 patients with schizophrenia, concurrent use of two or more antipsychotic medications quadrupled between 1995 and 1999 [9]. The addition of a FGA to a SGA has been advocated as a means of enhancing antidopaminergic blockade for the management of positive symptoms of psychosis. However, the evidence base for this practice is limited to anecdotal case reports and small, uncontrolled studies [9]. There is only one controlled, double-blind study of the effectiveness of antipsychotic polypharmacy. This study of 28 patients with a partial treatment response to clozapine found improvement in positive and negative symptoms for

augmentations with sulpirid compared to placebo [34]. An important body of literature has questioned antipsychotic polypharmacy, forwarding not only the high costs, but the loss of the beneficial propensities of SGAs on negative symptoms that are caused by their favourable receptor binding profile [10], as well as their increased risk of side effects, such as QT-prolongation or diabetes mellitus, and mortality [11]. Comedication, especially of SGAs with SSRIs, raises similar concerns about increased costs. In our survey, comedication was prescribed particularly in older schizophrenic patients suffering from comorbid diagnoses.

**Duration of antipsychotic maintenance treatment**

In our survey, we divided illness duration at the 2-year threshold. One important finding is that the investigated sample consists of a substantial part of schizophrenic patients with illness duration of above 2 years. It has been proposed that a first episode is followed by a "critical period" often lasting 2 years in which intervention may yield more beneficial results than later [35]. This method did not allow to control how many episodes each patient had. Thus, our finding that about as many psychiatrists maintain antipsychotic treatment in psychosis of less than 2 years duration for less than 2 years than for over 2 years, does not allow to draw any conclusive answers as to whether private psychiatrists maintain relapse treatment according to international guidelines in first episode patients. However, it is noteworthy that the indicated duration of maintenance treatment for patients with illness duration of above 2 years corresponded largely to recommendations of international guidelines. Earlier studies had suggested that a large number of psychiatrists not only scored significantly below the recommendations of the international guidelines [36], but that they often suggested no relapse prevention at all for first-episode patients. Psychiatrists seemed to underestimate the relapse risk and simultaneously overestimate the risk for adverse events and side effects [36]. An earlier Swiss study revealed that only 16% of 42 private psychiatrists would maintain antipsychotic relapse medication after a first schizophrenic episode between 12 and 24 months, and for at least 5 years in patients with multiple schizophrenic episodes [37]. Interestingly, our findings of good application of recommended maintenance treatment were unrelated to psychiatrists' socio-demographic variables such as years since graduating from medical school or region of practice.

**Non-compliance**

An important number of the schizophrenic patients included in our survey had a history of medication non-adherence. Non-compliance was twofold higher than medication non-adherence due to adverse events of side effects. Our findings suggest that non-compliance was correlated with polypharmacy and with more frequent psychiatric visits. Among non-compliant patients, more patients with comorbid substance use disorders and of younger age were found, which is in line with findings from earlier studies [15, 17]. It has been proposed that SGAs are superior to FGAs in terms of extra-pyramidal side effects and tardive dyskinesia [20] and thus contribute to better medication-adherence in schizophrenic patients [22, 23]. Our finding that more patients with a history of medication non-adherence and with an adverse event accounting for non-adherence were found in the group treated with SGAs is noteworthy and seems to be in line with a recent study which reported no preference of SGAs over FGAs in schizophrenic out-patients [38]. Our survey did not assess whether the indicated episode of non-compliance actually happened with the current antipsychotic treatment or with earlier, different treatment regimes. Therefore we were not able to refute the possibility that these episodes of non-compliance took place under treatment with FGAs. Alternatively, however, our findings may reflect that side effects emerging in the treatment with SGAs – such as sedation, weight gain or metabolic complications – and their impact on compliance may be underestimated and deserve more careful consideration.

## Conclusions

Our survey suggests that at least a sub-group of private psychiatrists in Switzerland conform to international treatment recommendations with regard to SGA use, monopharmacy and maintenance treatment. As mentioned above, the risk of including more pharmaco-biologically interested and "up-to-date" psychiatrists into this survey, may have resulted in a too positive estimate of the current treatment practice in Swiss private psychiatry. Alternatively, these results may be a consequence of the new policy among physicians' associations which constrains their members to participate in continuous educationprogrammes. The results may also reflect less restrictive mental health policies in Switzerland compared to other countries in terms of prescribing the costly SGAs. This may not only allow psychiatrists to become more familiar with the newer class of antipsychotics, but also enable them to become more familiar with international recommendations.

*Correspondence:*
*Andor E. Simon, M.D.*
*Clinical and Research Consultant Psychiatrist*
*Spezialsprechstunde zur Abklärung und*
*Behandlung psychotischer Frühphasen*
*Externe Psychiatrische Dienste Baselland*
*CH-4101 Bruderholz, Schweiz*
*E-Mail: andor.simon@tiscalinet.ch*

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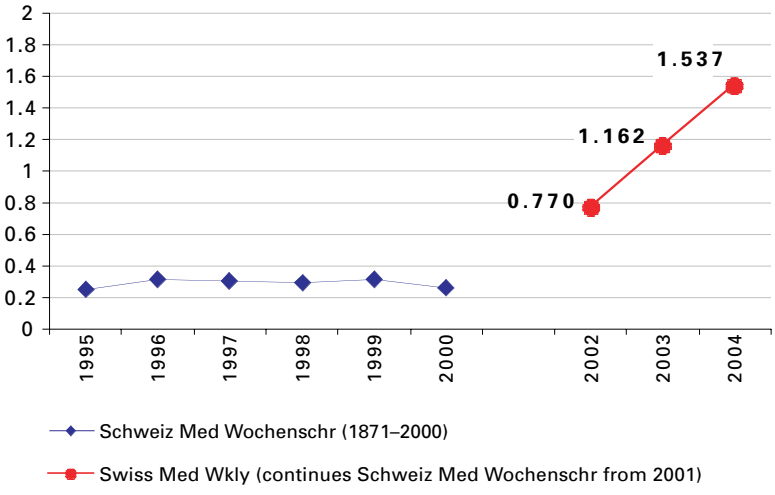


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