# Clinicians' Attitudes Toward the Use of Long-Acting Injectable Antipsychotics

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**Abstract:** Depot formulations are not widely used in everyday practice. This study aimed to assess psychiatrists' attitudes toward the use of long-acting injectable (LAI) antipsychotics in schizophrenia. We interviewed 113 French psychiatrists about the factors that influenced their prescription of LAI antipsychotics. Multidimensional and cluster analyses were used to detect correlations. The most important factor against the use of LAI antipsychotics is a sufficient estimated compliance with the oral formulation. For first-generation LAI, the main factor is the risk for extrapyramidal symptoms; and for second-generation LAI, it is the unavailability of the equivalent oral formulation. Four factors incite the psychiatrists to prescribe LAI. Two different clusters of patients can also be identified. Most factors influencing the clinicians' attitudes toward the use of LAI antipsychotics are shared in many countries. Conversely, some attitudes related to organizational aspects, particularly the relevance of health care costs, may vary from one country to another.

**Key Words:** Antipsychotics, long-acting injectable, attitudes, schizophrenia

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According to systematic reviews, between 40% and 60% of patients with schizophrenia are known to be partially or totally noncompliant to oral antipsychotic medication (Dolder et al., 2002; Valenstein et al., 2004). Poor adherence is associated with higher risk for relapse of schizophrenia and increased health care costs (Patel et al., 2008).

However, depot formulations are not widely used in routine practice, with a prescription rate of generally lower than 30% in different countries (Barnes et al., 2009; Patel and David, 2011). However, the use of long-acting injectable (LAI) formulations varies between countries. The prescription rates are higher in France (23.5%; Fourrier et al., 2000) and in the United Kingdom (29%; Barnes et al., 2009) compared with other European countries and with Canada (6.3%; Williams et al., 2006) or the United States (17.6%; West et al., 2008).

This discrepancy between countries can be considered to derive from the health care system and from the different attitudes displayed by psychiatrists.

Perceived coercion or presumed risks for lower tolerance of depot forms have been identified as factors responsible for this low use (Heres et al., 2006; Patel and David, 2011). More generally, negative attitudes from practitioners toward these forms have been shown to account for part of the low prescription rates of depot antipsychotics (Hamann et al., 2010; Heres et al., 2006, 2008, 2011).

The main goal of our study was to assess the attitudes of psychiatrists toward LAI antipsychotics in patients with schizophrenia to understand the reasons for using or not assigning depot treatment. We studied these attitudes in a sample of psychiatrists working in France using the same questionnaire that was used in a population of German psychiatrists (Heres et al., 2006, 2008). Our results will be discussed in the light of the data from the German studies.

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## METHODS

### Procedure and Instruments

At the French Congress of Psychiatry (November 17–20, 2010, Lyon, France), we questioned French psychiatrists about their attitudes toward depot antipsychotic treatment. We identified a randomized sample of 150 participants from the global list of participants (approximately 1500). Six raters were recruited to individually interview each randomized psychiatrist. All subjects participated with informed, voluntary, and written consent. When a participant refused, he/she was replaced by the next on the randomized list. We stopped inclusions at the end of the congress.

After acceptation, each psychiatrist was interviewed individually for 40 minutes using a single questionnaire devised by adapting questionnaires used in two separate studies conducted in different samples of German psychiatrists (Heres et al., 2006, 2008).

Demographic data were collected (age; sex; number of years of experience; and type of practice, *i.e*, hospital or independent).

Each psychiatrist estimated the percentage of patients followed up in the year 2010 and who were diagnosed with schizophrenia or schizoaffective disorder. Within this patient group, the percentages of patients treated with oral first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) and with LAI FGAs and SGAs were obtained. The psychiatrists estimated what percentage of their patients currently taking oral antipsychotics had a low compliance and accepted a prescribed depot formulation.

The psychiatrists in our sample were questioned about the factors that influenced, negatively or positively, the prescription of LAI antipsychotics. Misgivings about using depot formulations were assessed using a 14-item questionnaire. The degree to which each item influenced the decision to prescribe was scored on a 5-point Likert scale. We considered a minimum mean rating of 3 in either the FGA or the SGA category as threshold for the potential impact of a statement on a psychiatrist's decision against depot treatment.

A total of 14 items favorably influencing psychiatrists in the use of depot forms for schizophrenia were presented to the participants. The degree of influence of each item was evaluated on an 11-point scale, ranging from 0 (does not influence the prescription of depot forms) to 10 (very strongly influences the prescription of depot forms). The choice of an 11-point scale is related to the need to duplicate the German questionnaire to ensure comparability and the aim to reach a better level of discrimination between ratings in a domain that is difficult to assess.

For favorable and unfavorable factors alike, a distinction was made for each item between LAI formulation of FGAs and SGAs.

### Statistical Analysis

Descriptive data were presented using means and standard deviation for quantitative variables and proportion for qualitative variables.

For both questionnaires, means or rating per statement between FGAs and SGAs were tested using *t*-tests for paired samples with two-sided levels of significance of $p < 0.003$ (postanalyses Bonferroni's correction after normality assumption test).

Pearson's correlation coefficients were calculated for the 14 attributes of the questionnaire designed to evaluate the factors influencing psychiatrists in the use of LAI formulations for schizophrenia. The correlation matrix was transformed to measure distance with the metric multidimensional scaling (MDS). This method transforms a distance matrix into a set of coordinates. Using the (Euclidean) distances derived from these coordinates, we can approximate the original distances as accurately as possible. The MDS is used for visualizing correlational data; it plots the items on a map so that their correlational structure is accessible by visual inspection. The Proc MDS in Statistical Analysis System software was used to determine the graphic representation, the goodness to fit, and the screeplot. A nonmetric MDS has been conducted, leading to a two-dimension structure with a better goodness to fit and the same items distribution among clusters.

## RESULTS

### Participants

After 3 days of congress, the raters interviewed a total of 139 psychiatrists. One hundred thirteen psychiatrists (53 women and 60 men) accepted and took part in the survey (mean [SD] age, 43.3 [10.5] years; experience, 14.5 [10.9] years), and 26 psychiatrists refused. Most of the participants were hospital practitioners (84.1%), 6.2% have a private practice, and 9.7% combined the two types of practice. The mean (SD) percentage of patients with a diagnosis of schizophrenia or schizoaffective disorder followed up in 2010 by the interviewed practitioners was 33.5% (23.4%). Of these patients, the mean (SD) percentage of those treated with depot FGAs was 11.3% (13.8%); with oral FGAs, 18.6% (19.3%); with LAI SGAs, 18.9% (14.1%); and with oral SGAs, 62.9% (23.4%). The psychiatrists estimated that among their patients diagnosed with schizophrenia or schizoaffective disorder, the mean (SD) proportion of noncompliant patients was 44.7% (20.6%) and the mean (SD) proportion of all patients with psychosis treated, of those who would accept a depot form, was 45.8% (23.9%).

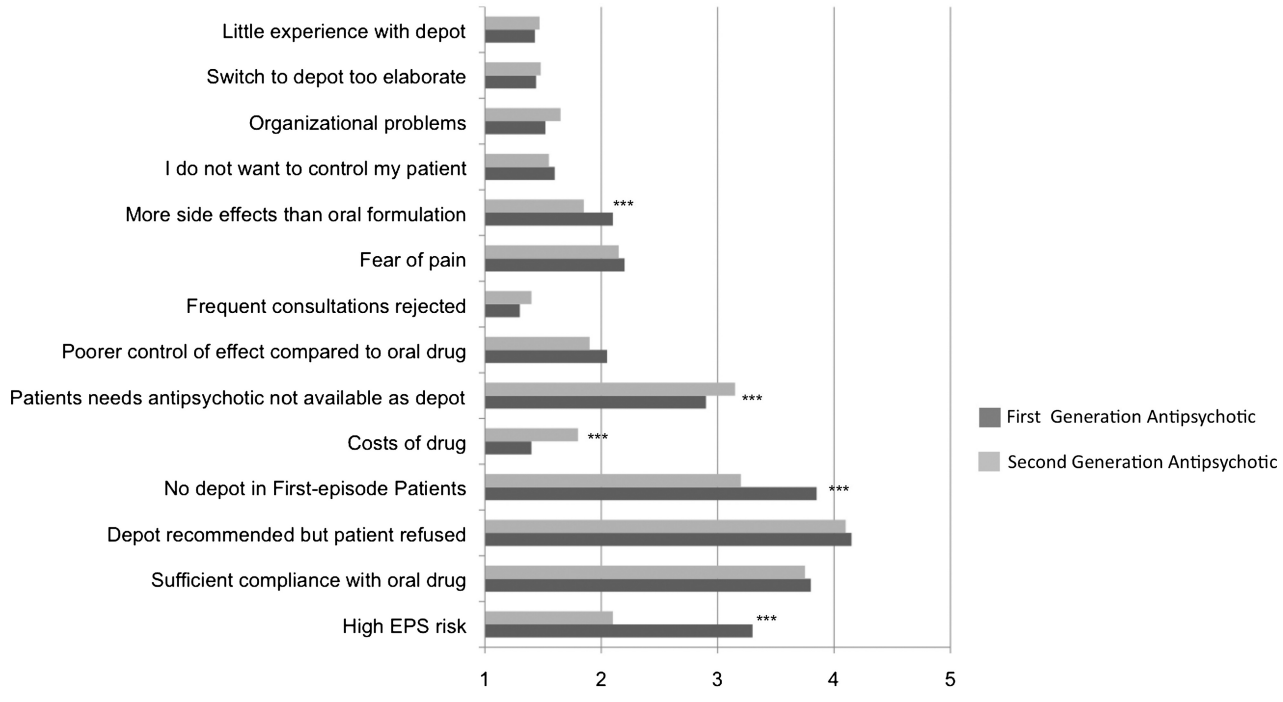
### Main Negative Factors Influencing Psychiatrists in the Prescription of Depot Antipsychotics

The main factors that affect a psychiatrist's decision against the use of LAI antipsychotics are shown in Figure 1. We look at the five factors for which the mean score was 3 points or more. In three of these, we found a statistically significant difference between FGA and SGA. The difference was statistically significant in disfavor of FGAs for high extrapyramidal symptoms (EPSs) risk and first psychotic episode, whereas the item unavailability of an equivalent of the oral antipsychotic in depot form was statistically more unfavorable to LAI SGAs than to depot FGAs.

No statistically significant difference was found between the two types of LAI formulation for the items sufficient compliance with oral drug and depot recommended but patient refused.

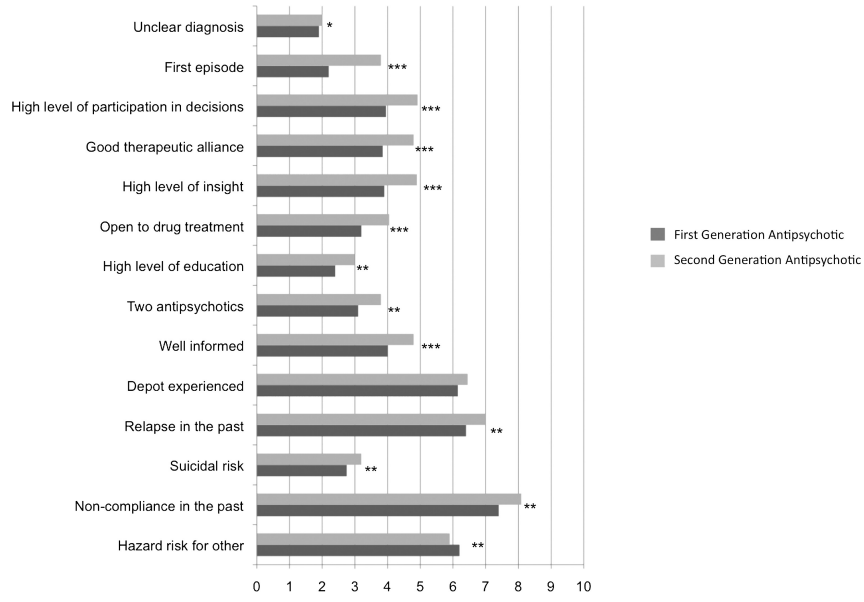
### Main Positive Factors Influencing Psychiatrists in the Prescription of Depot Antipsychotics

The highest scores representing an incentive for psychiatrists to prescribe LAI (Fig. 2) were the factors hazard risk for others, noncompliance in the past, relapse in the past, and depot experienced. A statistically significant difference was found between FGA and SGA for each of these four items. Hazard risk for others influenced the psychiatrists more for the prescription of FGAs than of SGAs. By contrast, the items noncompliance in the past, relapse in the past, and depot experienced favored the prescription of SGAs more than of




*** Paired ttest between FGA and SGA $P < 0.001$.

**FIGURE 1.** Extent of the influence of 14 statements on depot antipsychotic on decision against prescription of long-acting formulation in the treatment of schizophrenia.




Paired ttest between FGA and SGA: *$P$ < 0.05; **$P$ < 0.01; ***$P$ < 0.001.

**FIGURE 2.** Mean rating of the attributes potentially influencing the qualification for depot treatment.

FGAs. The items suicidal risk, high level of education, first psychotic episode, and unclear diagnosis exerted a low degree of influence on the decision of the psychiatrist to prescribe a depot form. There was a significant difference between the two classes, in favor of SGAs, for the items suicidal risk, and first psychotic episode.

An MDS analysis was carried out, distinguishing the data for FGAs from the data for SGAs. For depot forms of FGAs, the MDS points to a distribution of factors into two different clusters that are related to a positive influence on psychiatrists for the prescription of LAI (Fig. 3). The two-cluster configuration, taking into account only the results obtained for the LAI SGAs, also showed these two clusters, except for the item hazard risk for others, which, in this case, was found not to belong to cluster I.

## DISCUSSION

### Reasons for Nonuse of Depot Medication

The main reasons for not choosing an LAI antipsychotic, whichever the type (FGA or SGA), were that the patient refused and sufficient compliance with oral drug. These two factors are associated with mistaken beliefs held by psychiatrists.

Literature data are conflicting with regard to patient acceptance of depot forms. Several studies in the 1990s (Hoencamp et al., 1995; Pereira and Pinto, 1997; Wistedt, 1995) found a preference among patients for depot forms over oral forms at a time when the SGAs were still in low use and when there was no available LAI formulation of SGAs. In review (Walburn et al., 2001), the authors concluded that quality of data was poor, and surveys from representative samples of patients on maintenance antipsychotic medication were needed.

The psychiatrists questioned in our survey considered that 46% of patients would accept a depot form. In reality, a survey of patients with schizophrenia found that the acceptance rate of LAI in relapse prevention depended on their experience with this kind of formulation (Heres et al., 2007). Acceptance rates were 73% in patients currently being treated with depot, 45% in depot-experienced patients, and 23% in depot-naive patients.

The level of information from psychiatrists may thus contribute to the attitudes of patients toward depot forms and their acceptance rate. The psychiatrists estimate the acceptance rate to be 46%, which is possible, but they may offer it exactly to the wrong patients.

The psychiatrists also underestimated poor compliance rates (45% of patients) similar to those in the German study (44% of patients; Heres et al., 2008). This finding has been reported in several studies (Heres et al., 2008; Llorca, 2008; Remington et al., 2007). This belief is associated with the reluctance of psychiatrists to use depot antipsychotics when patients show good compliance with the oral drug form. Even worse—if psychiatrists really think that patients are poorly compliant, they still underuse depot in these patients (West et al., 2008).

Other deterrents to use depot medication seem to be related to the class of antipsychotic drug. Although depot FGAs are avoided because of a high risk for EPSs, LAI SGAs are less widely used because of a low availability of drugs such as aripiprazole, quetiapine, amisulpride, and clozapine. These two attitudes are associated because, in accordance with guidelines (Barnes, 2011; Falkai et al., 2006;

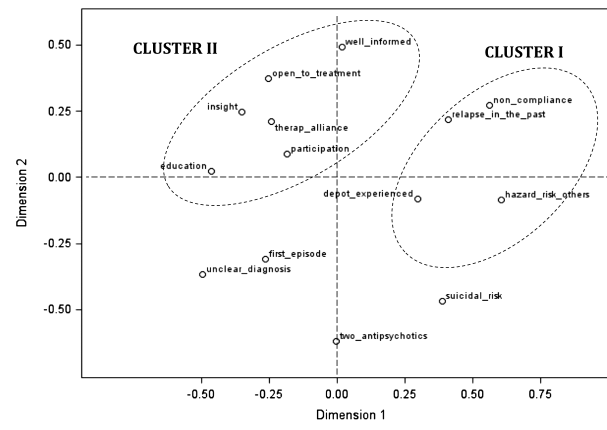



**FIGURE 3.** MDS analysis of correlation of ratings for LAI FGAs.

Kreyenbuhl et al., 2010), psychiatrists consider the safety-efficacy ratio of SGA as more favorable than FGA for first-line use. Recent or future registrations (by country) of olanzapine LAI and paliperidone palmitate and the development of depot aripiprazole could overcome this reluctance.

The practitioners questioned in this work emphasize first psychotic episode as a limiting factor in the use of depot forms. This result confirms those obtained from German psychiatrists (Fig. 5; Heres et al., 2006, 2011). Scientific data underlined that the use of LAI SGAs as early as the first psychotic episode offers many advantages in terms of efficacy and tolerance (Emsley et al., 2008a, 2008b; Kim et al., 2008). Improving adherence seems to be particularly important early on in the disease, with greater improvement in clinical outcomes in patients treated with risperidone LAI (RLAI) who were recently diagnosed with schizophrenia than in those with chronic schizophrenia (Olivares et al., 2009). Otherwise, recent studies demonstrated the superiority of RLAI, compared with the oral form, to maintain frontal lobe myelinization, to increase frontal lobe intracortical myelin, and to improve cognitive performance in the first psychotic episode (Bartzokis et al., 2011, 2012).

However, the available literature presents a weak level of evidence (open label, post hoc analysis, and small sample), and studies with high methodology quality are needed to confirm these results. This lack of evidence can explain the clinicians' negative attitudes toward LAI formulation.

A comparison of our results with those of the German surveys shows two main differences concerning reluctance to use depot forms (Fig. 4).

Firstly, the cost of drugs is not taken into account in the decision to prescribe a depot antipsychotic by French psychiatrists (although allowance for cost is significantly higher for LAI SGAs). In contrast, for German psychiatrists, the cost of LAI SGAs is a strong argument against their use. This difference can be explained by the specificity of the health care system in each country (*i.e.*, the French health care system recognizes schizophrenia as a "long-term disorder" qualifying for full health insurance cover with 100% reimbursement of drug costs).

Secondly, poorer control of effect with the depot form compared with the oral drug is considered by German psychiatrists, unlike the French, as a strong argument against using depot antipsychotics.

This difference in attitude is probably linked to the level of knowledge and habits of use of depot forms. Patel et al. (2009) emphasize the correlation between knowledge and attitudes in using depot antipsychotics. The training programs for young psychiatrists in the last 15 years (Heres et al., 2006) and habits of prescription of this form by older psychiatrists are probably different in France and in Germany.

## Factors Favoring the Prescription of Depot Forms

The MDS carried out on our results confirms the results obtained in a previous study (Heres et al., 2008), showing two clusters of factors preferentially taken into account by psychiatrists for the prescription of a depot form. Cluster I corresponds to patients with a history of relapse and poor compliance with oral forms. These patients present a less favorable medical prognosis, and this cluster corresponds to the classic profile of patients in whom depot forms are used. However, the occurrence of cluster II, corresponding to patients whose profile features a high level of insight and a high level of therapeutic alliance, is more unexpected. This cluster seems to be strongly opposed to cluster I, yet it is taken into account by the psychiatrists in the survey as decisive in

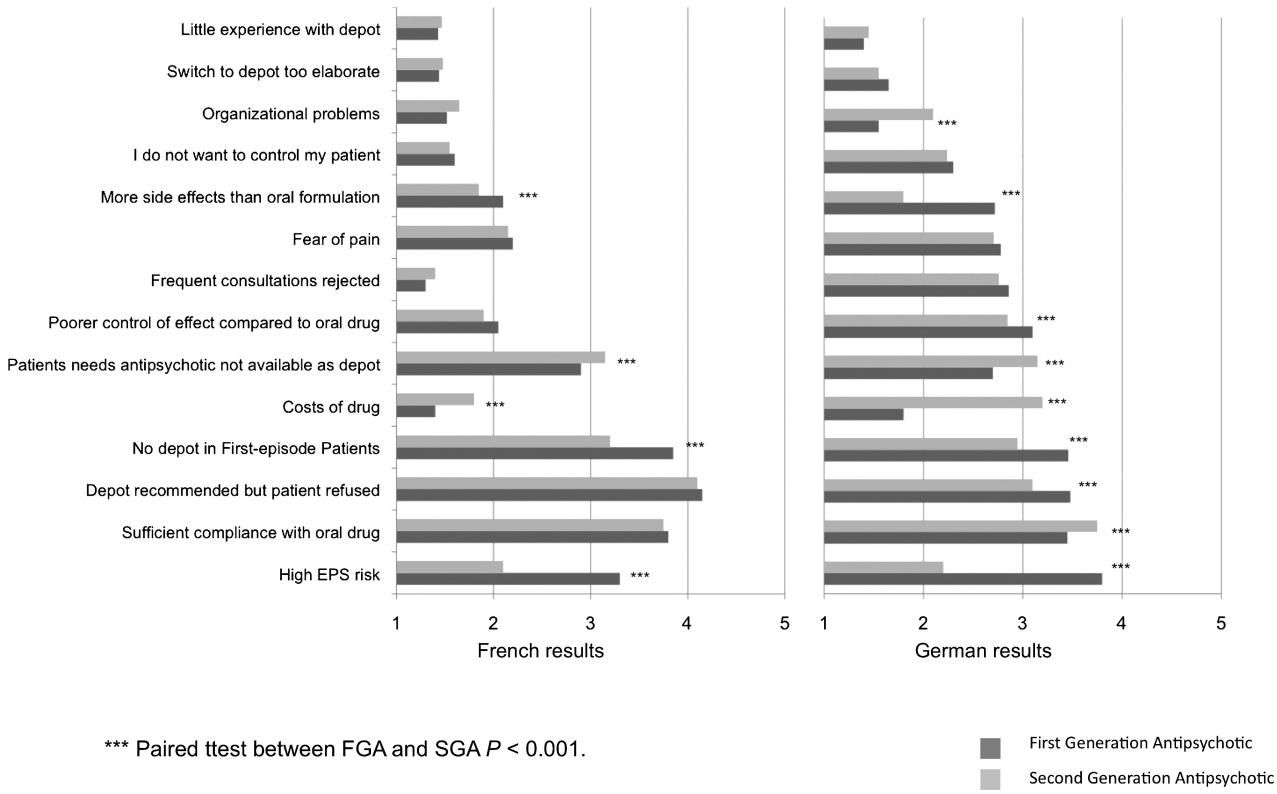



**FIGURE 4.** Mean rating of the attributes potentially influencing negatively the qualification for depot treatment. Comparison between French and German data (Heres et al., 2006).

prescribing a depot form. This cluster also doubtlessly corresponds to patients whose compliance with oral forms is probably the best (Llorca, 2008). We can readily suppose therefore that the impact of this cluster in the decision of the psychiatrist to use a depot form owes as much to the ease with which such patients can be informed about and convinced of the pharmacological utility of depot forms (in particular, more stable plasma levels) as to any expected gain in compliance (McEvoy, 2006). The usefulness of depot forms compared with oral treatment in terms of relapse prevention is not documented in this population category relative to the previous one (Heres et al., 2008). However, we note that even limited poor compliance with oral forms is enough to increase the risk for relapse considerably (risk for relapse multiplied by 2.81 for a non-compliance of only 11 to 30 days; Weiden et al., 2004).

It is also interesting to note that these two clusters appear for LAI formulation of both first and second generation. However, a difference was found for the SGAs, for which the factor hazard risk for others was not statistically correlated with the other factors in cluster I as it was for the FGAs. This finding suggests a preferential use of LAI formulations of SGAs for long-term treatment of schizophrenia, and use of FGAs may be more often prescribed for patients with behavioral disorders to curb impulsiveness and aggressiveness.

Risk for suicide did not appear to be a factor favorably influencing the participants in our study for the prescription of depot forms, in contrast to the results obtained in Germany (Fig. 5; Heres et al., 2008). It is hard to offer any convincing explanation for this difference. Even so, we can advance the hypothesis that a) a patient's impulse to act may carry greater weight for German psychiatrists and lead to a more ready recourse to depot forms and b) there is a more frequent evaluation of depressive comorbidity by French psychiatrists, leading to greater use of antidepressant treatments. To our knowledge, no drug epidemiological data are available by which this hypothesis could be tested. It implies different prescription habits linked to differences in psychiatric training provisions in the two countries. More generally, data on the utility of antipsychotics in reducing risk for suicide in patients with schizophrenia are, although appreciably favorable, still limited, except for clozapine, the only antipsychotic treatment approved by the Food and Drug Administration for this indication (Kasckow et al., 2011; Meltzer et al., 2003).

## Cultural Aspects

The organization of health care could be an important factor in shaping the attitude of psychiatrists toward depot forms and will differ between countries.

In France, psychiatric health care provision can be considered as quantitatively abundant, particularly in terms of equipment and human resources. Public hospital care makes up 80% of the psychiatric activity of health care providers, with a network organization based on the "psychiatric sector." It dispenses and coordinates all preventive and postcure care and rehabilitation over the surrounding geodemographic area. The 815 psychiatric sectors in France allow, in particular, the use of depot antipsychotics from outpatient services (medicopsychological centers) or part-time structures (day hospitals and part-time reception centers). This organization of health care facilitates the practical application of a depot antipsychotic prescription.

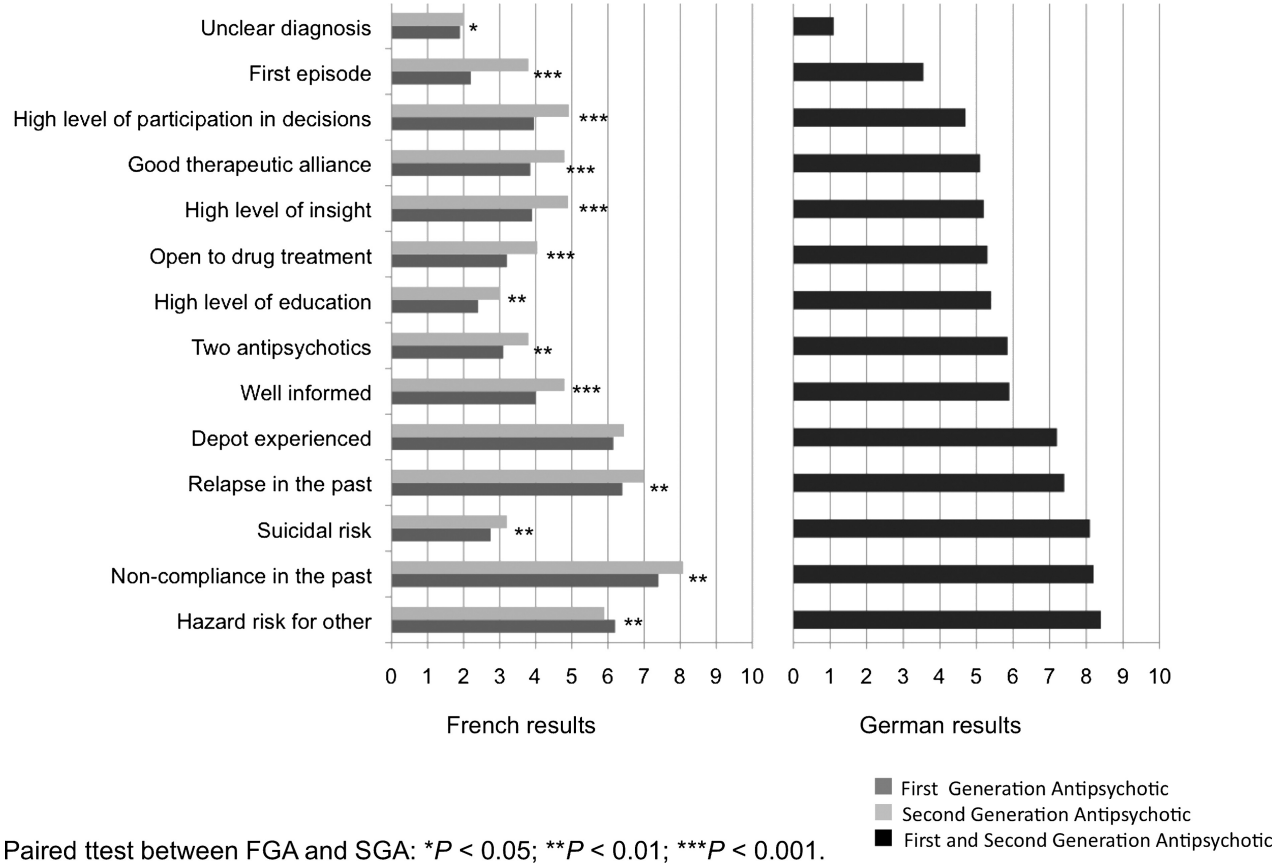



**FIGURE 5.** Mean rating of the attributes potentially influencing positively the qualification for depot treatment. Comparison between French and German data (Heres et al., 2008).

In Germany, patients with a psychiatric disorder can be treated either in specialized psychiatric hospitals or in psychiatric units within general hospitals. The total capacity of beds went down from 117.596 in the year 1972 (West Germany only) to 54.088 in the year 2005 (reunited Germany), also varying markedly between German districts (1.4/1000 inhabitants in Berlin to 0.4/1000 inhabitants in Sachsen-Anhalt). Outpatient treatment is offered by psychiatrists or neurologists in private practices; outpatient clinics; and specialized outpatient departments, so-called Psychiatrische Institutsambulanzen, which do offer additional treatment options apart from the sole physicians' care, for example, social workers, psychologists, or mental nursing staff. The specialized outpatient departments are not restricted in the use of antipsychotic drugs by a set budget, whereas the other outpatient facilities are limited in the amount of money they are allowed to spend for medication expenses. This leads to the situation that costly depot antipsychotics, mainly SGA in long-acting formulation, are underlying limitations in their use through these budget restrictions, in addition to other factors limiting their use.

Training of psychiatrists can also differ between countries and may affect their attitudes toward medication in clinical practice.

Nevertheless, if each country has its own health care system or training program, our results demonstrate that clinicians' attitudes toward LAI are rather similar.

### Limitations

The participants of our survey may be not necessarily representative of all psychiatrists. All participants were French psychiatrists, which limits our ability to generalize results within others countries.

No attempt was made to verify data on prescription rates or diagnosis frequency reported by the psychiatrists because the field of this study was on the subjective attitude toward depot treatment.

## CONCLUSIONS

We see that the attitudes of psychiatrists toward depot forms are somewhat negative, and their knowledge of them is patchy. However, the studies reported in the literature that compare relapse rates under oral and depot antipsychotics are highly favorable to depot forms. In an evidence-based clinical approach, psychiatrists should thus be systematically offering all patients with schizophrenia, in a shared decision making, a depot antipsychotic as first-line treatment. This is not what happens in practice, however, and the rate of prescription of these drugs is still low, although there are differences between countries. It seems that many factors are common in various countries (misgivings and positive attitudes). Conversely, attitudes connected with organizational aspects, particularly the relevance of health care costs, may vary from one country to another.

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## DISCLOSURES

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