Peer-reviewed version available at Int. J. Mol. Sci. 2016, 17, 1935; doi:10.3390/ijms17111935

Article

Clinical Decision-Making in the Treatment of Schizophrenia: Focus on Long-Acting Injectable Antipsychotics

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Abstract: The purposes of this study were to identify clinician's characteristics associated with higher prescription rates of long-acting injectable (LAI) antipsychotics, as well as the information sources influencing medical decision-making about treatment of schizophrenia. We surveyed 202 psychiatrists during 6 regional French conferences (Bordeaux, Lyon, Marseille, Nice, Paris, Strasbourg). Data on the characteristics of practice, prescription rates of antipsychotic and information sources about their clinical decisions were collected. Most of psychiatrists used second-generation antipsychotic (SGA), and preferentially an oral formulation, in the treatment of schizophrenia. SGA LAI was prescribed to 30.4% of schizophrenic patients. The duration and the type of practice did not influence the class or formulation of antipsychotics used. The clinicians following the higher percentage of schizophrenic patients were associated with the higher use of LAI antipsychotics and the lower use of oral SGA. Personal experience, government regulatory approval and guidelines for the treatment of schizophrenia were the 3 main contributing factors guiding the clinical decision-making of clinicians about treatment of schizophrenia. The more clinicians follow schizophrenic patients, the more they use LAI antipsychotic. The development of specialised programmes with top specialists should lead to better use of LAI in the treatment of schizophrenia.

Keywords: long-acting injectable; antipsychotic; decision-making; guidelines; schizophrenia

1. Introduction

Schizophrenia is a chronic illness with a high risk of relapse that is frequently associated with treatment discontinuation. Ensuring treatment adherence is one of the principal challenges in schizophrenia management. This requires awareness of several risk factors (e.g. symptoms of the illness, stigmatisation, poor therapeutic alliance, complex medication schedule) [1].

The development of long-acting injectable first-generation antipsychotics (LAI FGA) in the 1960s, and, more recently, of long-acting injectable second-generation antipsychotics (LAI SGA), has been an important step in the management of schizophrenia. These formulations are considered as one of the most efficacious pharmacological interventions available to address adherence problems in patients suffering from schizophrenia [2,3]. They offer several advantages, including transparency of adherence and possibility of early intervention of healthcare professionals if patients fail to take

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their medication, as well as, from a pharmacokinetic perspective, more consistent bioavailability and reduced peak-trough plasma levels [2,4].

LAI FGAs and LAI SGAs have proved to be effective in long-term treatment of schizophrenia, with the specific impact of reducing the relapse risk [4]. While the efficacy of LAIs compared with placebo in randomised clinical trials (RCTs) is well established, the evidence for the specific advantage for LAI SGAs over oral medication remains unclear [5,6]. The effectiveness of LAI has been debated, due to some inconsistent findings in the literature, in comparison to results about oral formulation treatments. The benefits of LAIs are significant in observational or mirror-image studies, however, they failed to reach statistical superiority in RCTs [3,7]. Study design seems to be an important factor. One possible explanation is that RCTs don't reflect the reality of clinical practice (patients who consent to participate are willing to be more involved in the care process and have better adherence) [7].

For a long time, the use of LAI has been reserved for patients with chronic illness and poor adherence. However, recent guidelines for the use and management of LAI antipsychotics in clinical practice evoke the possibility of using this formulation for patients with first-episode or recent-onset schizophrenia [8-12]. Despite most clinicians regarding them as effective, reported LAI prescribing rates are low [13] and vary widely between countries (6-30%) [14]. This highlights the barriers that exist to prescribing these formulations.

We hypothesise that there are some characteristics in clinicians' practice that might be associated with different modalities of prescription of LAI. The aims of our study were to identify (i) the characteristics of practice associated with higher prescription rates of LAI antipsychotic, and (ii) the sources of information influencing the medical decision-making regarding treatment of schizophrenia.

2. Materials and Methods

2.1. Procedure

We conducted a cross-sectional survey among psychiatrists during 6 regional conferences (Bordeaux, Lyon, Marseille, Nice, Paris, Strasbourg) of the French Society for Biological Psychiatry and Neuropsychopharmacology between December 2014 and April 2015.

We identified a randomised sample of 250 participants from the global list of participants (approximately 500). Recruitment of clinicians took place during each conference. All subjects participated with informed, voluntary and written consent.

The procedures followed in the study were approved by an independent national ethics committee (CPP Sud-Est 6) and were conducted in accordance with the revised version of the Helsinki Declaration (1989).

2.2. Assessments

A self-administered questionnaire was completed anonymously and returned at the end of conference by each participating psychiatrist.

The questionnaire comprised 3 sections:

- Demographic characteristics and characterisation of practice (gender, age, duration of career, type of practice, proportion of schizophrenic patients follow-up),
- Estimation of prescription rates of antipsychotics by the psychiatrists (oral FGA oral SGA, LAI FGA and LAI SGA)
- Sources of information influencing the medical decision-making about treatment of schizophrenia. Clinicians had to grade the sources of information proposed (i.e. published clinical studies, guidelines for the treatment of schizophrenia, information from congress or conferences, government regulatory approval, my personal experience) from 1 (first-line source) to 5 (last-line source).

2.3. Statistical analysis

Means and standard deviation were calculated for continuous measures and categorical data were presented as frequencies. Correlations analyses of type of antipsychotic used in schizophrenic patients and practice characteristics of clinicians were performed using Spearman correlations. Inter-group comparisons, according to the sources of information influencing the decision-making about treatment, were performed using the Wilcoxon–Mann–Whitney test.

Statistical analyses were performed using SAS 9.3_ software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-tailed and the significance level was set at 5%.

3. Results

3.1. Participants

A total of 202 psychiatrists participated in the survey (Table 1). The mean age and career duration were 43 ± 11 years and 13 ± 11 years, respectively. The majority of clinicians treated outpatients and inpatients. Almost half of the patients followed by clinicians (46 %) were treated for schizophrenia. Most of patients received SGA and preferentially oral formulation (55 %). Clinicians declare to prescribe LAI SGA to 30 % of their patients.

Table 1. Sample of participating psychiatrist (N = 202)

	n (%)
Gender (males)	97 (48.0)
	Mean ± SD
Age (years)	42.8 ± 11.4
Duration of career (years)	13.0 ± 10.7
Type of practice (%)	
Outpatient	55.4 ± 29.1
Inpatient	60.2 ± 27.2
Proportion of schizophrenic patients followed (%)	46.3 ± 24.3
Prescription of antipsychotics (% of schizophrenic patients)	
Oral FGA	16.2 ± 13.2
Oral SGA	54.9 ± 21.7
LAI FGA	13.6 ± 12.2
LAI SGA	30.4 ± 19.3

Abbreviations: FGA: first-generation antipsychotic; LAI: long-acting injectable; SGA: second-generation antipsychotic

3.2. Modalities of prescription according to the practice characteristics of clinicians

Table 2 shows the correlations between the type of antipsychotic used and the practice characteristics of clinicians. The class and the formulation of the antipsychotics were not influenced by the duration of clinicians' career or their type of practice. The higher the percentage of schizophrenic patients followed by clinicians, the more LAI antipsychotics (FGAs and SGAs) were used and the less oral SGAs were used.

Table 2. Correlations between type of antipsychotic used in schizophrenic patients and practice characteristics of clinicians.

	Career duration (years)		**% of inpatients**		**% of schizophrenic patients**	
	r	p-value	r	p-value	r	p-value
Oral FGA	0.10	0.23	0.04	0.60	0.06	0.41
Oral SGA	0.04	0.65	-0.07	0.33	-0.25	**< 0.01**
FGA LAI	0.11	0.16	0.01	0.94	0.35	**< 0.01**
SGA LAI	0.04	0.62	0.05	0.51	0.27	**< 0.01**

Abbreviations: FGA: first-generation antipsychotic; LAI: long-acting injectable; SGA: second-generation antipsychotic; r: Pearson correlation coefficient.

Table 3. Decision making about treatment according to the practice characteristics of clinicians.

		Career duration, mean (year) (SD)		% of inpatients, % (SD)		% of schizophrenic patients, % (SD)	
			p-value		p-value		p-value
Published clinical study literature	Yes	11.1 (10.2)	0.47	41.2 (35.6)	0.64	38.0 (25.7)	0.09
	No	12.7 (10.6)		50.3 (32.6)		47.2 (23.9)	
Guidelines for the treatment of schizophrenia	Yes	10.2 (9.6)	0.11	46.7 (30.4)	0.64	52.0 (23.0)	**0.05**
	No	13 (10.8)		49.8 (33.9)		43.5 (23.5)	
Information from congress or conferences	Yes	16.1 (13.0)	NA*	51.0 (38.7)	0.86	28.9 (24.2)	NA*
	No	12.3 (10.4)		49.1 (32.7)		47.1 (24.0)	
Government regular approval	Yes	11.4 (9.0)	0.68	48.3 (35.7)	0.89	49.4 (25.4)	0.36
	No	12.9 (11.1)		49.4 (31.9)		45.0 (23.9)	
Personal experience	Yes	15.4 (11.8)	**0.03**	55.1 (30.4)	0.13	44.1 (22.0)	0.61
	No	11.3 (9.8)		46.5 (33.7)		46.5 (25.3)	

*NA : statistical test non applicable

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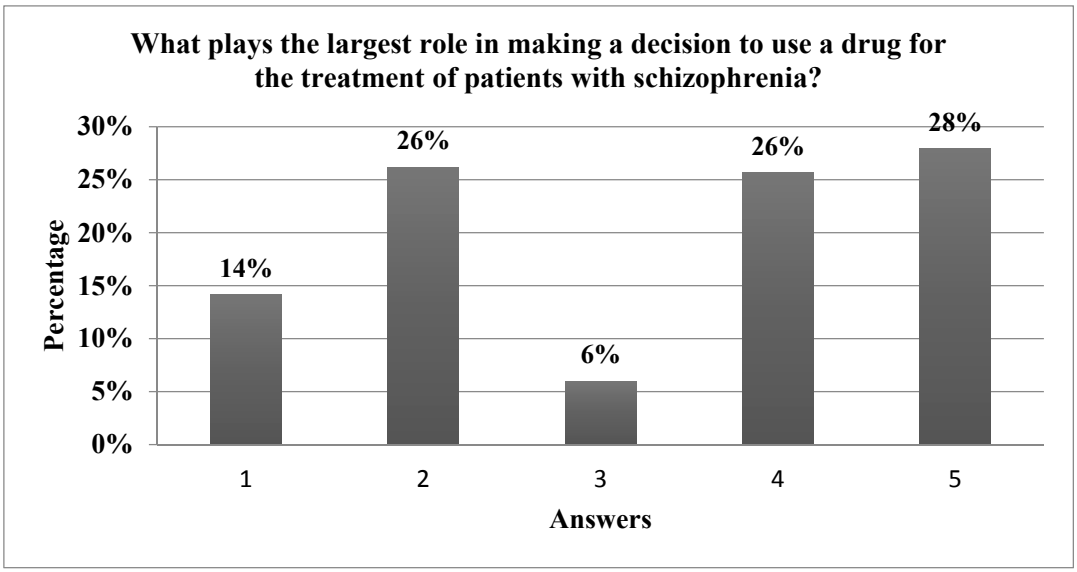
3.3. Modalities of decision-making about treatment of schizophrenia

Personal experience, government regulatory approval and guidelines for the treatment of schizophrenia were the 3 main contributing factors guiding the clinical decision-making of clinicians about treatment of schizophrenia (Figure 1). Published clinical studies only played the largest role as primary source in selection of appropriate therapy in 14% of clinicians, while information from congress or conferences played the largest role in 6% of clinicians,.

There were some differences in the factors influencing the clinical decision-making of psychiatrists about treatment according to their practice characteristics (Table 3). Personal experience, as the main factor guiding clinical decision-making, was significantly associated with higher career duration of clinicians ($p = 0.029$). Use of guidelines for the treatment of schizophrenia was significantly associated with a higher proportion of schizophrenic patients in the follow-up of clinicians ($p = 0.049$).

Figure 1. Factors influencing the medical decision-making about treatment of schizophrenia.



Answers

1. Published clinical study literature
2. Guidelines for the treatment of schizophrenia
3. Information from congress or conferences
4. Government regulatory approval

4. Discussion

In this naturalistic sample of French psychiatrists, practitioners declare that more than 30% of their treated schizophrenic patients received LAI SGA.

Specifically, our findings showed that:

- Clinicians treating the highest proportion of schizophrenic patients prescribed significantly more LAI antipsychotics and less oral SGAs.
- Other clinicians' practice characteristics were not significantly associated with a differential use of LAI antipsychotics.
- Personal experience, government regulatory approval and guidelines for the treatment of schizophrenia were the main factors guiding the clinical decision-making of clinicians in the choice of the type and formulation of antipsychotic prescribed.

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Career duration appeared to be associated with decision making about treatment based on the personal experience of psychiatrists. Conversely, the proportion of schizophrenic patients seemed to be associated with an evidence-based decision making of clinicians (using guidelines for the treatment of schizophrenia).

Psychiatrists reported prescribing SGA (oral and LAI) for most of their schizophrenic patients, as recommended as first-line treatment by guidelines for the management of schizophrenia [15]. The prescription rate of LAI formulation appeared higher in comparison with other studies, which found prescription rates of generally lower than 30% [16,17]. However, there is a possible lack of correspondence between the prescription rates reported and every day practice (as described by prescription study [18]). Psychiatrists probably overestimated their real use of LAI in clinical practice.

Among the practice characteristics of psychiatrists involved in this study, only the proportion of schizophrenic patients was significantly associated with the prescription of LAI. Clearly, the higher the percentage of schizophrenic patients followed by clinicians, the more LAI formulations were used. Previous studies showed that clinicians with more experience of LAI provided more information about LAI to their patients, as well as having more favourable attitudes toward LAI than the psychiatrists with less experience [19,20]. They also obtain significantly higher acceptance rates of LAI in patients [20]. On the other side, factors, such as limited knowledge and experience with LAI, negative attitudes toward LAI and prescribing practices reducing the use of LAI as a "last-resort" for patients with past history of non-adherence, should limit the use of LAI by psychiatrists [21]. This suggests that there is probably a virtuous circle between level of experience in treating schizophrenia patients, level of experience in LAI use and attitudes toward LAI and prescription rate of these formulations.

There was no significant correlation between the type of antipsychotic used (class or the formulation) and the other characteristics of clinicians (age, duration of career and type of practice). In contrast, a previous study showed that "older" psychiatrists offered and prescribed significantly more LAI FGA and less LAI SGAs than their "younger" colleagues [22]. A possible explanation is that the recent development of SGA LAI formulations, offering numerous equivalences with oral SGA (olanzapine, risperidone, paliperidone, aripiprazole), has facilitated their use independently of the age of clinicians or their career duration, due to the better benefits–risks ratio than FGA LAI.

It is worth mentioning that factors influencing the decision-making about the treatment of schizophrenia mainly combined experience and evidence-based medicine. In comparison with a previous French study, we noted a steep increased in the use of guidelines in clinical practice from 12.5%, in 2007-2008, to 26%, in the present study [23]. One hypothesis could be that the recent development of specific French guidelines for the use and management of LAI antipsychotic in serious mental disorders [11,24], using a consensus-based methodology involving practitioners, facilitated their adherence and their use in clinical practice. The primarily reasons given for the non-use of guidelines by French psychiatrists were related to the cultural differences between Anglo-Saxon practice and French practice, and related to the distinction between expert and practitioner psychiatrists [23]. Moreover, the implementation of educational regional workshops in France following their publication probably also helped to promote their use, as highlighted by a recent Cochrane systematic review [25].

The level of experience in treating schizophrenic patients also appeared to be significantly more correlated with the use of treatment guidelines. If guidelines have been established to help clinicians to make their choice of appropriate care in specific clinical circumstances, most of them have been developed for specific psychiatric disorder (e.g. schizophrenia, bipolar disorder, anxiety disorders…). Clearly, general psychiatrists cannot spend the necessary time to read all of the different guidelines (and their updates) from the different agencies or societies for all the serious mental disorders. Consequently, the fact that more specialised psychiatrists in schizophrenia used guidelines for the treatment of schizophrenia in clinical practice more frequently makes sense.

These points highlight the need to develop specific strategies to provide optimal care for patients with schizophrenia. In the United States (Texas), the potential solution was the creation of the A ShoT At Recovery (A-STAR) program. In this organisation, the aim of the integrated team is to enhance the

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use of LAI medication by providing data and education, both to prescribers and patients [26]. In France, the development and implementation of the Schizophrenia Expert Centers (Fondation FondaMental) should have the same impact. Clinicians working in this organisation develop a hyper-specialisation in treating schizophrenia. The goal of this network is to promote an evidence-based but personalised medicinal approach, and to provide the best therapeutic strategies for each patient to obtain remission and reduce the risk of relapse [27].

The main limitation of this study is the cross-sectional design that did not allow analysis of the causal relationships between type of antipsychotic used and the practice characteristics of clinicians. Another relevant issue that the participants may not necessarily be representative of all French psychiatrists due to a possible selection bias. Gender distribution of the participating psychiatrists was close to the national values published by the French National Medical Council (50% males, 50% females), however, our survey involved younger psychiatrists than the national mean age (43 vs 51 year old) [28]. Finally, no attempt was made to verify data on prescription rates or diagnosis frequency reported by the psychiatrists.

5. Conclusions

Despite recent evidence showing the benefits of the use of LAI antipsychotics early in the course of management of patients with schizophrenia, the gap with their use in clinical practice stays wide. Numerous barriers, including overestimation of patient's adherence, patient refusal or perceived coercion, have previously been identified. However, no effective strategies have reduced these barriers and changed the prescribing behaviour of psychiatrists. Our findings highlight the significance of the current development of Expert Centers or specialised programmes in the management of schizophrenic patients, as well as patients with other serious mental disorders, in many countries. `

Acknowledgments: The authors thank all the participants for the time they spent on this survey and the French Society of Biological Psychiatry and Neuropsychopharmacology.

Author Contributions: LS and PML designed the study and wrote the protocol. LS and MG wrote the first draft of the manuscript and collected the data. CA performed the statistical analyses. The manuscript was critically reviewed by all of the authors. All authors read and approved the final manuscript.

Conflicts of Interests: Dr Samalin received grants, honoraria, or consulting fees from AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, and Takeda.
Dr Garnier received grants, honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Otsuka.
Pr Llorca received grants, honoraria, or consulting fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, and Takeda.
Auclair C. have no financial or other potential conflicts of interest.

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