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ORIGINAL ARTICLE

Pattern of use of clozapine in Spain. Variability and under-prescription☆

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Clozapine;
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Abstract
Introduction: International studies on clozapine use usually show lower than expected prescription proportions, under-dosing and delayed initiation of treatment, which has led to a number of initiatives aimed at improving its use and reducing the striking variability observed among practitioners. There are no similar studies on the Spanish population. Therefore we planned initial data collection from 4 territorial samples. We hypothesised that clozapine prescription would also be low and variable in our country. If this hypothesis were confirmed, a reflection on possible strategies would be necessary.
Material and methods: We accessed data on clozapine prescription in Catalonia, Castile and Leon, the Basque Country and the Clinical Management Area of the Hospital 12 de Octubre (Madrid).
Results: Patients diagnosed with schizophrenia under treatment in these territories comprise around .3% of their total population; treatment with clozapine ranges between 33.0 and 57.0 per 10,000 inhabitants; patients diagnosed with schizophrenia on current treatment with clozapine range between 13.7% and 18.6% of the total number of patients with this diagnosis. The coefficient of variation between centres and prescribers is often higher than 50%.

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Conclusions: Although below the figures suggested as desirable in the literature, global prescribing data for clozapine in the areas we studied are not as low as the data collected in other international studies, and are in the range of countries in our environment. However, the variability in prescription is large and apparently not justified; this heterogeneity increases as we focus on smaller areas, and there is great heterogeneity at the level of individual prescription.
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PALABRAS CLAVE
Clozapina;
Esquizofrenia;
Prescripción;
Variabilidad

Patrón de uso de clozapina en España. Variabilidad e infraprescripción

Resumen
Introducción: Los datos internacionales disponibles sobre uso de clozapina recogen en general una baja prescripción, infradosificación y retraso en el inicio del tratamiento, y han originado diversas iniciativas para mejorar su uso y disminuir la llamativa variabilidad. No disponemos de estudios que valoren estos aspectos en población española, por lo que nos hemos planteado una primera y modesta aproximación a través de 4 muestras territoriales. Nuestra hipótesis es que, al igual que las referencias comentadas, en nuestro país el consumo de clozapina podría ser bajo y variable. Nuestro objetivo, en caso de confirmarse la hipótesis, sería iniciar una reflexión sobre posibles estrategias a plantear.
Material y métodos: Los autores han accedido a datos de consumo de clozapina en Cataluña, Castilla y León, País Vasco y un Área de Madrid (el Área de Gestión Clínica PSM del Hospital 12 de Octubre).
Resultados: Los pacientes con diagnóstico de esquizofrenia en tratamiento en los territorios estudiados oscilan en torno al 0,3%; los tratamientos con clozapina/10.000 habitantes entre el 33% y 57%; y los pacientes diagnosticados como esquizofrenia en tratamiento con clozapina suponen entre el 13,7% y 18,6% de los tratados. El coeficiente de variación entre centros y prescriptores es frecuentemente superior al 50%.
Conclusiones: Aunque por debajo de las cifras indicadas por la literatura, los datos globales de prescripción de clozapina en los territorios que hemos estudiado no son tan bajos como los recogidos en otros trabajos internacionales, y se sitúan en el rango de países de nuestro entorno. Sin embargo, la variabilidad en la prescripción es muy importante, aparentemente no justificada; y aumenta a medida que analizamos zonas menores, hasta una gran heterogeneidad de la prescripción individual.
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Introduction

Although conceptually challenged[1] the psychotic syndrome which for a century we have being calling schizophrenia continues to be the paradigm of mental illness.[2] Treatment with antipsychotic drugs (AP) partially helps to alleviate some of its symptoms and is considered a necessary part of more complex procedures.[3] However these drugs are also prone to intense and prevalent reflection.[4–7] The first generation of AP has been replaced by the so-called ''atypical antipsychotics'' (AA).[8] Despite the fact the concept of being ''atypical'' is confusing, no difference in efficacy has been demonstrated,[9–13] and the uniformity of the AA group is unsustainable[14–18] New AP drugs have increased in consumption exponentially on the acceptance of new indications, or due to their off-label use.[19,20]

Clozapine was the first AP classified as ''atypical'', based on its mechanism of action, which was a non-provoker of catalepsy in animal models, or of extrapyramidal effects in patients. These elements were mimicked in its design or at least in its marketing by the AA drugs that followed in its wake.

Global efficacy data on schizophrenia suggest the superiority of clozapine compared with other AP[13,15,21–27]; specifically compared with the first generation of these drugs,[21,14] and in general with the rest of the so-called ''atypical'' antipsychotics.[10,18,25,28–30] Readmittance rates with clozapine are low[31–34] and adherence is higher than that of other AP,[32,35,36] as is also cognitive performance, level of employment activity, independent living and voluntary treatment.[37,25] Clozapine is particularly effective in some differentiated situations, such as risk of suicide in schizophrenia,[38–42] aggression in psycosis[43] and reduction in the consumption of toxic substances in patients who have been diagnosed with schizophrenia.[44–46] It is also effective in bipolar disorder[47,48] and in psychosis in patients with Parkinson's disease.[49]

The absence of the expected response to appropriately administered drugs over time and doses is currently called ''resistant schizophrenia'' and is observable in 18%–30%

of cases.[50–54] This concept is highly questionable for its simplification, which focuses on the so-called ''positive symptoms'' and does not consider grading in response levels,[55–56] highly varied prevalence,[5,58] resulting in very recent studies reminding us of the need for independent studies from the sector and finally with inclusion criteria and homogeneous assessment tools,[59] particularly with regard to follow-up.[14,60] In this type of situations, clozapine presents itself as clearly superior to other substances,[10,24,28,51,54,61–64] with symptomatic response rates of around 60%–70%[65] and is the only substance approved for this indication.[53]

In the present framework of open challenge to mass, indiscriminate and undefined use of AP,[6,5] beyond the simplistic descriptive perspective of ''resistance'' the neurobiological substrate of which we follow without realising[66] clozapine is proposed as an alternative[4] in patients who do not respond to the standard D2 blocking of AP,[67,68] or when they appear to drop in efficacy over time and mass use, possibly related to a situation of secondary hypersensitivity to a process of receptorial overregulation.[69,57,70]

Clozapine is not risk-free, but this has to be appropriately brought into proportion. Rigorous haematological monitoring has meant that with a prevalence of agranulocytosis estimated to be 1.3%,[71–73] the rate of mortality would be .1%–.3%. The rate of diabetic ketoacidosis varies between 1.2% and 3.1%, and gastrointestinal hypomotility is 4%. Interest in myocarditis is increasing, incidence rates between countries are imbalanced, with a worldwide mean of .02%–1%. In Australia it is 7%, no doubt due to the stricter monitoring.[71,74,75] As a whole, clozapine could be associated with lower overall mortality compared with any other AP,[76–78] always lower than the risk of death from schizophrenia.[38]

Consumption of clozapine is lower than predicted conceding its indications.[79–81] Specifically, the proportion of patients diagnosed with schizophrenia who receive clozapine is usually lower than the expected resistance percentages expressed[79,82–88]: 6.7% in Québec,[80] 10.2% in Denmark,[89] 12.7% in India, or 11% in Hong Kong[90] as examples, rising to 23% in England and Wales.[91,92] In general, usage rates of clozapine have increased over the past decade,[90,93] and there has only been a drop in prescription in Colombia and in the population with pubic insurances in U.S.A.[94] where, in 1999[86] 6.1% of patients with this diagnosis received clozapine, 5.7% in 2006; 4.9% in 2007; 4.6% in 2008; and 4.3% in 2009.[95] In 2014 the population of U.S.A. with private insurance policies was, together with Japan, the country with the lowest rates of prescription (14/100,000 inhabitants and .6/100,000 respectively). This opposite extreme to Finland (189.2/100,000) and New Zealand (116.3/100,000) is extraordinary.[94]

Clozapine prescription ranges between 1% and 2% of the total AP in many countries,[96] but geographical variability is highly relevant. Thus in U.S.A the difference between states ranges from 2% in Louisiana to 15.6% in South Dakota.[88,97] In Quebec, regional differences range between 3.9% and9%[80] and in Great Britain, the raised variability between regions in the National Health System drastically dropped between 2000 and 2006, after definition of guides in this respect[98] and the drop in prices.[99] In a very recent international analysis, there was a 315 times factor difference between the countries studied.[94]

Protocols and guidelines regarding dose and indication criteria[3,100–102] are systematically not complied with, delaying the beginning by a mean of 5 years,[84,89,103–106] and 8.9 years in males.[35,107] During this time the largest proportion of patients(68%[35]) received multiple AP and combinations despite the little evidence to sustain this practice,[86,103] worsening the prognosis and increasing the risks.[108] Prescription is not just low and late, it also appears to be arbitrary on occasions or conditioned by racial factors.[109–111] Manuel et al. found in New York that, surprisingly, drug consumption is associated with a lower prescription of clozapine and coloured people and those of Hispanic descent receive it less than white people,[112] This tendency is replicated throughout the U.S.A.[88] Age and gender also condition access to the drug: young people and women globally receive lower prescriptions of clozapine than men aged between 40 and 59 years.[94] Finally under-dosing is frequent,[53] and not only in standard care, where doses are rarely customised using plasmatic levels, but also in trials which compare clozapine to other drugs.[12,113] Unlike the succession of approvals of new indications for the other AA, the specific indications shown for clozapine, such as the risk of suicide, drug consumption or aggression, are not officially accepted.

As a whole, the available international data indicate general low prescription, under-dosing and delay in treatment initiation. There are no available studies to assess these aspects in the Spanish population and we therefore proposed an initial approach with 4 territorial samples. Our hypothesis was that, similar to the references already commented upon, the consumption of clozapine in Spain could also be low and variable. Should this hypothesis prove to be true, our aim was to stimulate reflection on possible strategies.

Material and methods

The authors were able to gain access to consumption data regarding clozapine in Catalonia, Castile Leon, the Basque Country and an Area of Madrid (the Clinical Psychiatry and Mental Health Management Area of Hospital 12 de Octubre, AGCPSM H12O), with a higher detail level in the Basque Country and Madrid. Here, apart from consumption in patients diagnosed with schizophrenia during a temporary period, subterritories were able to be differentiated (provinces of the Basque Country, Mental health centres of Usera, Villaverde and Carabanchel) and even professionals in the last case. The source in the case of Catalonia was ''Salut Mental i Addiccions Resum executiu 2015, Xarxa de Salut Mental de Catalunya''; in the Basque Country it was ''The use of clozapine in el treatment of patients with schizophrenia in the CAV Project''; in Castile Leon and in Madrid the source were data from the AGCPSM H12O and the pharmacy service of these areas.

Results

Table 1 shows the overall results.

Table 1 Global results.

		Benchmark population 2015	Pat.Dd.Schitz. attended	Pat.Dd.Schitz. in tmt/100 inhab	Tmts cloza	Tmts cloza/100,000 inhab	% Pat.Dd.Schitz. with clozapine
2015 Catalonia	(*See graph. AMHC*)	**6,109,571**	**22,142**	**.36**	**3033**	**49.6**	**13.7**
2017 Basque Country	Vizcaya	1,138,852	3122	.27	776	68.1	16.17
	Guipúzcoa	710,699	1910	.26	317	44.6	12.25
	Álava	322,335	503	.15	213	66.08	17.30
	Total	**2,171,886**	**5535**	**.22**	**1306**	**59.59**	**15.24**
[2015 H12O Area	Usera	132,744	512	.38	104	78.3	20.31
	Villaverde	140,599	378	.26	82	58.3	21.69
	Carabanchel	240,230	386	.16	46	19.1	11.91
	Total	**491,129**	**1276**	**.25**	**232**	**47**	**17.9**
2016 Castile Leon	Valladolid	523,679			104	19.8	
	Segovia	155,652			33	21.2	
	León	473,604			153	32.3	
	Salamanca	335,985			114	33.9	
	Zamora	180,406			63	34.9	
	Ávila	162,514			65	39.9	
	Burgos	360,995			160	44.3	
	Palencia	164,644			75	45.5	
	Soria	90,040			42	46.6	
	Total	**2,447,519**			**809**	33	

AMHC: adult mental health centre, Catalonia; Pat.Dd.Schitz.: patients diagnosed with schizophrenia attended; Tmts cloza: treatments with clozapine.

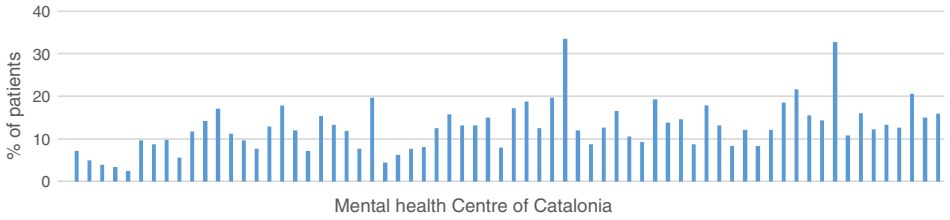

Figure 1 Percentage of patients diagnosed with schizophrenia in treatment with clozapine in the mental health centres for adults of the Mental Health Network of Catalonia 2015.

Catalonia

Considering the population of reference in Catalonia in 2015 was 6,109,571 inhabitants, the rate of diagnosis of schizophrenia would amount to .36%; and the rate of treatment with clozapine to 4.9 per 10,000 inhabitants.

13.7% of the patients in treatment for a diagnosis of schizophrenia in Catalonia in 2015 received treatment with clozapine (11.6% women, 15% men), with a variation coefficient between centres above 50%, as reflected by the graph. This is a pharmaceutical prescription quality objective of the Mental Health Network of Catalonia (Fig. 1).

Basque Country

Considering the population of the Basque Country in 2017 was 2,171,886 inhabitants, there were 5535 people in treatment diagnosed with schizophrenia, which amounts to .22% of the population (.26% in Guipúzcoa; .27% in Vizcaya and.15% in Álava).

In July 2017 there were 1306 patients in treatment with clozapine throughout the Basque Country, with no specified diagnoses. As a whole, the rate of treatments with clozapine in the autonomous community of the Basque Country would be 59.59/100,000 inhabitants, although their distribution was not uniform and the rate in Vizcaya was 68.1 treatments/100,000 inhabitants, in Guipúzcoa 44.6 and in Álava 66.08.

If we consider the patients in treatment diagnosed with schizophrenia and the number of treatments with clozapine, rates range between 12.25% of patients treated with this drug in Guipúzcoa, 17.30% in Álava, 16.17% in Vizcaya, with a mean of 15.24%.

Castile Leon

We only obtained the number of patients being treated with clozapine in each province in 2016, deducing the rate of treatments according to the population which, globally, was situated at 3.30/10,000 inhabitants, with some differences between provinces (from 1.98 in Valladolid to 4.66 in Scoria).

Hospital 12 de Octubre, Madrid Area

The population attended in the whole of the H12O Madrid Area in 2015 was 491,129 inhabitants, 137,914 in Usera, 156,527 in Villaverde, and 196,688 in Carabanchel. Diagnostic rates for schizophrenia amounted to .25% (.37% in Usera; .24% in Villaverde; .19% in Carabanchel) and treatment rates with clozapine were 4.7/10,000 (5.9/10,000 in Usera; 5.2/10,000 in Villaverde; 2.3/10,000 in Carabanchel).

Seventeen point ninety seven per cent of patients in treatment after diagnosis of schizophrenia in the whole area received treatment with clozapine in 2015 (20.31% in Usera, 21.69% in Villaverde, and 11.1% in Carabanchel), as is reflected in Table 1.

The daily defined dose (according to the Collaborating Centre for Drug Statistics Methodology regulations) prescribed in 2015 in the H12O Area by the psychiatric specialists in the mental health centres (extra hospital treatment units which take on practically all the specialised follow-ups but do not include the primary care prescriptions), range between 10,239 and 20,963 in the districts mentioned, representing between 11.36% and 18.26% of the total AP indicated, as reflected in Table 2.

Within the same centre, the difference in prescription between specialists responsible for similar patient profiles was also notable (Fig. 2).

Discussion

Overall clozapine prescription data in the territories studied are not as low as those reflected in other international studies and they are similar to those in the range of neighbouring countries. However, the variability in prescription is highly pronounced and this increases as we analyse smaller areas, entailing great diversity of individual prescription.

As we mentioned between 18% and 30% of patients diagnosed with schizophrenia will comply with the standard resistance criteria, and would be candidates for receiving clozapine. Of these 60%–70% would respond to the drug, and we should therefore find minimum rates of 20% of patients in treatment for this diagnosis, receiving clozapine.[114]

Although this minimum is not reached, overall data are close in H12O (17.9%); to a lower extent in the Basque Country (15.24%) and Catalonia (13.7%). These levels are above some of the countries referred to but very different from the British or the New Zealand data. However, these figures would vary notably when we observe the smaller territories: the 3 Basque Country provinces range between 17.30% in Álava, 16.17% in Vizcaya and 12.25% in Guipúzcoa; variations are very similar in the 3 districts of H12O: 21.69% in Villaverde, 20.31% in Usera, and 11.91% in Carabanchel. In Cataluña the differences between adult mental health centres ranged between .0% and 33.5%.

The notable variability between Spanish territories with no major socio-demographic differences, with a common usage guideline for clozapine and with a similar proportion

Table 2 Daily defined dose of antipsychotics prescribed in mental health centres of the AGCPSM H12O.

Functional unit	DDD clozapine	DDD AP	% Clozapine/total AP
MHC-Usera	20,963	114,779	18.26
MHC-Villaverde	17,223	95,158	18.10
MHC-Carabanchel	11,598	109,572	10.58
Total non-inpatient activity	49,794	3,195,010	15.64

AGCPSM H12O: Clinical Psychiatry and Mental Health Management Area of Hospital 12 de Octubre; AP: antipsychotics; MHC: mental health centres; DDD: daily defined dose.

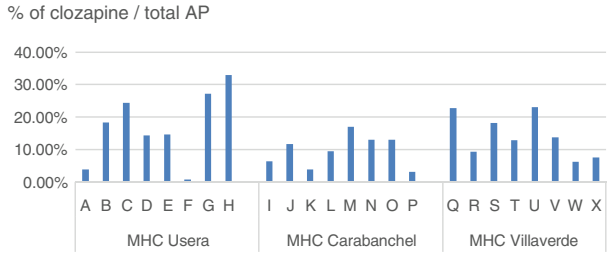

Figure 2 Prescriptions by specialists in mental health centres (MHC) of Usera, Carabanchel and Villaverde.

of patients in treatment after diagnosis of schizophrenia (between .22% and .36% – lower than the theoretically expected prevalence of .5%–.7%[115]) is confirmed when, instead of patients in treatment, we study prescriptions. Overall, Spanish treatment rates with clozapine/100,000 inhabitants range between 33 and 59/100,000 inhabitants which are similar to countries such as France (43.1), Italy (41.8), Denmark (58k3) or Norway (50.1); but very different from New Zealand (116.3) or Holland (103.1); and very different from theoretical standards (200/100,000 inhabitants).[94]

However, as we analyse the prescriptions in smaller territories, variability increases, Thus, in Castile Leon the differences between provinces range from 19.8 to 46.6/100,000 inhabitants; in the Basque Country from 44.6 to 68.1/100,000 inhabitants. The proportion of clozapine treatments (daily defined doses) compared with the total AP which we found in the H12O districts ranged from 18.26% or 18.10% in Usera and Villaverde to 10.58% in Carabanchel. When we analysed prescription from different specialists, with similar consultation profiles and uniformity of population in number and quality, the differences between them rose to between .88% and 33.03% in the same centre.

Variability in practice is not exclusive to psychiatry,[116,117] nor does it only affect drug prescription.[118] On occasions, economic, social and cultural circumstances may condition that variability. We thus find the important change in the prescription of clozapine in England after the availability of cheaper generic drugs,[99] or a drop in usage in China which although still high due to lower price and different usage regulations,[119] is dropping in the most developed provinces and in families with a higher purchasing power level.[120,121] In U.S.A. the use of clozapine in patients with private healthcare is low compared with the state system. This is probably due to the low number of patients who would be likely to be treated with clozapine, who work and therefore are able to have private healthcare.[94] We believe in our case that although we have studied territories with undeniable sociocultural and economic differences, the weight of these factors is unable to explain the variability, and particularly if we observe that the highest differences are found in the smaller territories, such as the mental health centres for adults in Catalonia and even among prescribing practitioners of the same district in the case of H12O.

Although diversity does not explain our data, it is also striking in the regulations which govern the use of the drug in different countries, and which is proposed as the cause of the differences. Several factors are variable, including authorisation from the GP for prescribing it, availability of non-oral formulations, supply from normal pharmacies, maximum authorised dose, and the definition of ''resistant'' schizophrenia. Most of these differences do not have a clear clinical justification and there is a striking imbalance in access to the drug. However, although it seems probable that the restrictive regulations dissuade practitioners and patients from using the treatment, at least with regulations as extreme as those in Japan (which presents .6 treatments/100,000 inhabitants),[94] there are no objective data regarding the effect of the different regulations in consumption,[122] and it cannot be considered the essential factor, as illustrated in the case in Colombia, without restriction of usage by indications and without demand for haematological control, but with modest prescriptions.[94]

With regard to the general Spanish prescription framework, the AP market radically changed from the 1990s onwards, with the eruption of new drugs designed under its influence,[55] without its risk,[123] and which were initially believed to be as effective as clozapine. The new AP drugs have displaced the market of their predecessors despite their higher price,[124–127] with aggressive marketing campaigns compared with the low economic interest in clozapine.[88] These facts could partially account for prescription variability.[111]

Notwithstanding, although less defined than the previous factors those most frequently related to usage variability are as crude as that of the tradition in using a treatment in a certain territory, and the differences in criteria and knowledge of the prescribers.[88,95] In the case of Spain, the relative social uniformity of the territories studied, the identity of a legal framework, and the increase in differences as we approach the prescriber's individual level leads us to believe that these are the factors with the most impact on our findings.

To date, few empirical research studies have been conducted on the reasons for underprescription of clozapine by psychiatrists.[128] The arguments generally put forward are complications imposed by regulations, lack of expertise

in management and fear of side effects by practitioners, patients or family members.[129] The perception of risk in practitioners is disproportionate,[114] and parallel to the lack of knowledge on usage.[130,131]

In recent years several different initiatives have been put into practice by the state bodies of several countries, which propose a use of clozapine adjusted to the patient volume which, with the appropriate risk–benefit balance, could benefit from treatment.[95] These actions appear in the Clozapine Collaboration Group (DCCG), promoting a guide and other actions between professionals and patients. In 2014 a 56% increase in clozapine treatments had been achieved.[114] In New Zealand between 2000 and 2004 the use of clozapine in patients with a diagnosis of schizophrenia increased from 21% to 32.8%.[10,15,31] In 2010 the Best Practices Initiative—Clozapine was started in New York state. This developed facilitating actions for the prescribers and tools of assistance in the election for patients, in the framework of a shared decision model. New prescriptions increased by 40% between 2009 and 2013.[132]

The definition of a clear framework of knowledge is the necessary basis but is insufficient. Purely didactic approaches have little impact on the physician's behaviour,[133] and it has been suggested that even the guidelines act as a further barrier.[122] Actions need to be implemented at all healthcare levels, involving mental and general health teams, political actors and patients and family members[28,134] with state support,[135–137] using comprehensive care models with care support coordination systems for treatment implementation. The creation of specific devices[131] is controversial. With regard to the law, despite being extraordinarily restrictive it is not complied with, and its solid grounding varies in different countries. An initiative needs to be generated to provide consistency to regulations[122] and ensure their compliance.

It would be interesting to establish educational programmes for professionals, but also for patients and family members, provided this was within the framework of comprehensive care, shared decisions, care coordination and support for decision and implementation.[131,138] To this end an initiative was developed in 2016 in the AGCPSM H12O, the aim of which was to promote appropriate use of clozapine. The initial stage, in keeping with this analysis of the prescription situation, consisted in the development of a practical usage guide for clozapine adapted to Spain, distributed through several actions among all Area professionals. A centralised, homogenous system was also organised for collection of accessible haematological protocols from any point in the network, including in the emergency unit. A second phase is to extend into primary care in a customised manner between patients and family members, with the use of specific material. The effects of these actions on prescription are to be studied.

Limitations

As previously mentioned, this study was only intended as an initial action to motivate other broader and more uniform qualitative studies, and actions for correct prescription, should this be necessary. Although we consider that the main conclusions on global usage and variability are valid, the source of the data is multifarious in several aspects: the collection dates are different: Catalonia and the Basque Country collect prescription data in patients diagnosed with schizophrenia whilst although probably most prescriptions are for this diagnosis, the H12O does not specify this. Also, prescription data for the Basque Country and H12O refer to non-hospital activity. Catalonia offers us global data. Unlike the Basque Country, the prescription data from Catalonia and H12O refer to specialised care, without taking into account any prescriptions from in each territory. The data from Castile Leon only refer to prescriptions, with no consideration of diagnosis. We propose these differences be resolved in further, broader studies.

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Conflict of interests

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References

1. Van Os J. ''Schizophrenia'' does not exist. BMJ. 2016;352:i375, http://dx.doi.org/10.1136/bmj.i375.
2. Berrios GE, Fuentenebro de Diego F. Delirio: historia. Clínica. Metateoría. Madrid: Trotta; 1996.
3. National Institute for Health and Care Excellence (NICE). Psychosis and schizophrenia in adults: prevention and management. Clinical guideline. Available from: nice.org.uk/guidance/cg178 [published 12.02.14; accessed 29.03.18].
4. Murray RM, Quattrone D, Natesan S, Van Os J, Nordentoft M, Howes O, et al. Should psychiatrists be more cautious about the long-term prophylactic use of antipsychotics? Br J Psychiatry. 2016;209:361–5, http://dx.doi.org/10.1192/bjp.bp.116182683.
5. Inchauspe JA, Eizaguirre AV. Uso de antipsicóticos en la psicosis. Alcance, limitaciones y alternativas. Rev Asoc Esp Neuropsiquiatr. 2017. Cuaderno T:1–63.
6. Mcgorry P, Alvarez-jimenez M, Killackey E, Alvarez-Jiménez M. Antipsychotic medication during the critical period following remission from first-episode psychosis: less is more. JAMA Psychiatry. 2013:8–10, http://dx.doi.org/10.1136/bmj.c4024.3.

7. Wunderink L, Nieboer R, Nienhuis F, Sytema S, Wiersma D. Long-term outcome following early dose-reduction of antipsychotics in remitted first episode psychosis. Schizophr Bull. 2015.
8. Prah P, Petersen I, Nazareth I, Walters K, Osborn D. National changes in oral antipsychotic treatment for people with schizophrenia in primary care between 1998 and 2007 in the United Kingdom. Pharmacoepidemiol Drug Saf. 2012;21:161–9, http://dx.doi.org/10.1002/pds.2213.
9. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ. 2000;321:1371–6, http://dx.doi.org/10.1136/bmj.321.7273.1371.
10. Jones PB, Barnes E, Davies TR, Dunn G, Lloyd H, Hayhurst KP, et al. 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. 2006;63:1079–89, http://dx.doi.org/10.1001/archpsyc.63.10.1079.
11. Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet (London, England). 2008;371:1085–97, http://dx.doi.org/10.1016/S0140-6736(08)60486-9.
12. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553–64, http://dx.doi.org/10.1001/archpsyc.60.6.553.
13. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373:31–41, http://dx.doi.org/10.1016/S0140-6736(08)61764-X.
14. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatry. 2016;73:199–210, http://dx.doi.org/10.1001/jamapsychiatry.2015.2955.
15. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry. 2009;166:152–63, http://dx.doi.org/10.1176/appi.ajp.2008.08030368.
16. Leucht S, Kissling W, Davis JM. Second-generation antipsychotics for schizophrenia: can we resolve the conflict? Psychol Med. 2009;39:1591–602, http://dx.doi.org/10.1017/S0033291709005455.
17. Naber D, Lambert M. The CATIE and CUtLASS studies in schizophrenia: results and implications for clinicians. CNS Drugs. 2009;23:649–59, http://dx.doi.org/10.2165/00023210-200923080-00002.
18. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382:951–62, http://dx.doi.org/10.1016/S0140-6736(13)60733-3.
19. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Utilización de Antipsicóticos en España (1992-2006). Available from: https://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/antipsicoticos.pdf [accessed 28.03.18].
20. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. Psychiatr Serv. 2009;60:1175–81, http://dx.doi.org/10.1176/ps.2009.60.9.1175.
21. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry. 1999;156:990–9, http://dx.doi.org/10.1176/ajp.156.7.990.
22. Tuunainen A, Wahlbeck K, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia. Cochrane Database Syst Rev. 2000, http://dx.doi.org/10.1002/14651858.CD000966. CD000966.
23. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophr Res. 2002;56:1–10 [Internet].
24. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006;163:600–10, http://dx.doi.org/10.1176/appi.ajp.163.4.600.
25. Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, et al. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010, http://dx.doi.org/10.1002/14651858.CD006633.pub2. CD006633.
26. Souza JS, Kayo M, Tassell I, Martins CB, Elkis H. Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses. CNS Spectr. 2013;18:82–9, http://dx.doi.org/10.1017/S1092852912000806.
27. Kane JM, Correll CU. The role of clozapine in treatment-resistant schizophrenia. JAMA Psychiatry. 2016;73:187–8, http://dx.doi.org/10.1001/jamapsychiatry.2015.2966.
28. Davis D, Evans M, Jadad A, Perrier L, Rath D, Ryan D, et al. The case for knowledge translation: shortening the journey from evidence to effect. Br Med J. 2003;327:33–5, http://dx.doi.org/10.1136/bmj.327.7405.33.
29. Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, et al. Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. Health Technol Assess. 2006;10, iii–iv, ix–xi, 1–165.
30. Lobos CA, Komossa K, Rummel-kluge C, Hunger H, Europe PMC Funders Group. Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2014:1–281, http://dx.doi.org/10.1002/14651858.CD006633.pub2.
31. Rose D, Fleischmann P, Wykes T. Consumers' views of electroconvulsive therapy: a qualitative analysis. J Ment Health. 2004;13:285–93, http://dx.doi.org/10.1080/09638230410001700916.
32. Tiihonen J, Walhbeck K, Lönnqvist J, Klaukka T, Ioannidis JPA, Volavka J, et al. 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. 2006;333:224, http://dx.doi.org/10.1136/bmj.38881.382755.2F.
33. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:603–9, http://dx.doi.org/10.1176/appi.ajp.2011.10081224.
34. Tiihonen J, Mittendorfer-Rutz E, Majak M, Mehtälä J, Hoti F, Jedenius E, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia. JAMA Psychiatry. 2017, http://dx.doi.org/10.1001/jamapsychiatry.2017.1322.
35. Alessi-Severini S, le Dorze JA, Nguyen D, Honcharik P, Eleff M. Clozapine prescribing in a Canadian outpatient

population. PLOS ONE. 2013;8:8–11, http://dx.doi.org/10.1371/journal.pone.0083539.
36. Sanz-Fuentenebro J, Taboada D, Palomo T, et al. Randomized trial of clozapine vs. risperidone in treatment-naïve first-episode schizophrenia: results after one year. Schizophr Res. 2013;149:156–61, http://dx.doi.org/10.1016/j.schres.2013.07.003.
37. Wheeler A, Humberstone V, Robinson G. Outcomes for schizophrenia patients with clozapine treatment: how good does it get? J Psychopharmacol. 2009;23:957–65, http://dx.doi.org/10.1177/0269881108093588.
38. Walker AM, Lanza LL, Arellano F, Rothman KJ. Mortality in current and former users of clozapine. Epidemiology. 1997;8:671–7 [Internet].
39. Duggan A, Warner J, Knapp M, Kerwin R. Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. Br J Psychiatry. 2003;182:505–8 [Internet].
40. Meltzer HY, Baldessarini RJ. Reducing the risk for suicide in schizophrenia and affective disorders. J Clin Psychiatry. 2003;64:1122–9 [Internet].
41. Alphs L, Anand R, Islam MZ, Meltzer HY, Kane JM, Krishnan R, et al. The international suicide prevention trial (interSePT): rationale and design of a trial comparing the relative ability of clozapine and olanzapine to reduce suicidal behavior in schizophrenia and schizoaffective patients. Schizophr Bull. 2004;30:577–86 [Internet].
42. FDA. ''Clozaril'' Prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019758s062lbl.pdf [accessed 29.03.18].
43. Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry. 2006;63:622–9, http://dx.doi.org/10.1001/archpsyc.63.6.622.
44. Green AI, Zimmet SV, Strous RD, Schildkraut JJ. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry. 1999;6:287–96 [Internet].
45. San L, Arranz B, Martinez-Raga J. Antipsychotic drug treatment of schizophrenic patients with substance abuse disorders. Eur Addict Res. 2007;13:230–43, http://dx.doi.org/10.1159/000104886.
46. Marín-Mayor M, López-Álvarez J, Francisco López-Muñoz GR. Clozapine use in dual diagnosis patients. J Clin Med Res Update. 2014;1:11–20.
47. Ifteni P, Correll CU, Nielsen J, Burtea V, Kane JM, Manu P. Rapid clozapine titration in treatment-refractory bipolar disorder. J Affect Disord. 2014;166:168–72, http://dx.doi.org/10.1016/j.jad.2014.04.020.
48. Nielsen J, Kane JM, Correll CU. Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. Bipolar Disord. 2012;14:863–9, http://dx.doi.org/10.1111/bdi.12018.
49. Fernandez HH, Donnelly EM, Friedman JH. Long-term outcome of clozapine use for psychosis in parkinsonian patients. Mov Disord. 2004;19:831–3, http://dx.doi.org/10.1002/mds.20051.
50. Lieberman JA. Pathophysiologic mechanisms in the pathogenesis and clinical course of schizophrenia. J Clin Psychiatry. 1999;60 Suppl. 1:9–12 [Internet].
51. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry. 2001;158:518–26, http://dx.doi.org/10.1176/appi.ajp.158.4.518.
52. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. Biol Psychiatry. 2001;50:898–911 [Internet].
53. Farooq S, Taylor M. Clozapine: dangerous orphan or neglected friend? Br J Psychiatry. 2011;198:247–9, http://dx.doi.org/10.1192/bjp.bp.110.088690.
54. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. Am J Psychiatry. 2016;173:166–73, http://dx.doi.org/10.1176/appi.ajp.2015.15030332.
55. Weiden PJ. How many treatments before clozapine? Medication choices across the spectrum of treatment resistance in schizophrenia. J Clin Psychiatry. 2016;77:e594–6, http://dx.doi.org/10.4088/JCP.16com10797.
56. Sanz Fuentenebro FJ, Artaloytia Usobiaga JF, Molina Rodríguez V, Palomo Álvarez T. Esquizofrenia ''resistente''. Conceptos confusos y tratamientos esperanzadores. Psiquiatr Biol. 2001;8:11–8.
57. Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graff-Guerrero A, et al. Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. Psychiatry Res. 2012;197:1–6, http://dx.doi.org/10.1016/j.psychres.2012.02.013.
58. Schooler NR, Marder SR, Chengappa KNR, Petrides G, Ames D, Wirshing WC, et al. Clozapine and risperidone in moderately refractory schizophrenia: a 6-month randomized double-blind comparison. J Clin Psychiatry. 2016;77:628–34, http://dx.doi.org/10.4088/JCP.13m08351.
59. Howes OD, McCutcheon R, Agid O, De Bartolomeis A, Van Beveren NJM, Birnbaum ML, et al. Treatment-resistant schizophrenia: treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017;174:216–29, http://dx.doi.org/10.1176/appi.ajp.2016.16050503.
60. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2016;209:385–92, http://dx.doi.org/10.1192/bjp.bp.115.177261.
61. Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ, Okasha A, Singh B, et al. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res. 2008;100:20–38, http://dx.doi.org/10.1016/j.schres.2007.11.033.
62. Wehmeier PM, Kluge M, Schneider E, Schacht A, Wagner T, Schreiber W. Quality of life and subjective well-being during treatment with antipsychotics in out-patients with schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry. 2007;31:703–12, http://dx.doi.org/10.1016/j.pnpbp.2007.01.004.
63. Schneider C, Corrigall R, Hayes D, Kyriakopoulos M, Frangou S. Systematic review of the efficacy and tolerability of clozapine in the treatment of youth with early onset schizophrenia. Eur Psychiatry. 2014;29:1–10, http://dx.doi.org/10.1016/j.eurpsy.2013.08.001.
64. Vanasse A, Blais L, Courteau J, Cohen AA, Roberge P, Larouche A, et al. Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real-world observational study. Acta Psychiatr Scand. 2016;134:374–84, http://dx.doi.org/10.1111/acps.12621.
65. Agid O, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. J Clin Psychiatry. 2011;72:1439–44, http://dx.doi.org/10.4088/JCP.09m05785yel.

66. Gillespie AL, Samanaite R, Mill J, Egerton A, MacCabe JH. Is treatment-resistant schizophrenia categorically distinct from treatment-responsive schizophrenia? A systematic review. BMC Psychiatry. 2017;17:12, http://dx.doi.org/10.1186/s12888-016-1177-y.
67. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry. 2012;169:1203–10, http://dx.doi.org/10.1176/appi.ajp.2012.12010144.
68. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, et al. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry. 2014;75:e11–3, http://dx.doi.org/10.1016/j.biopsych.2013.06.011.
69. Oda Y, Kanahara N, Iyo M. Alterations of dopamine D2 receptors and related receptor-interacting proteins in schizophrenia: the pivotal position of dopamine supersensitivity psychosis in treatment-resistant schizophrenia. Int J Mol Sci. 2015;16:30144–63, http://dx.doi.org/10.3390/ijms161226228.
70. Suzuki T, Kanahara N, Yamanaka H, Takase M, Kimura H, Watanabe H, et al. Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. Psychiatry Res. 2015;227:278–82, http://dx.doi.org/10.1016/j.psychres.2015.02.021.
71. Citrome L, McEvoy JP, Saklad SR. A guide to the management of clozapine-related tolerability and safety concerns. Clin Schizophr Relat Psychoses. 2016, http://dx.doi.org/10.3371/CSRP.SACI.070816.
72. Pons A, Undurraga J, Batalla A, Bernardo M. Clozapine and agranulocytosis in Spain: do we have a safer population? A 5-year hematologic follow-up. Rev Psiquiatr Salud Ment. 2012;5:37–42, http://dx.doi.org/10.1016/j.rpsm.2011.11.003.
73. Capllonch A, de Pablo S, de la Torre A, Morales I. Increase in white cell and neutrophil counts during the first eighteen weeks of treatment with clozapine in patients admitted to a long-term psychiatric care inpatient unit. Rev Psiquiatr Salud Ment. 2016, http://dx.doi.org/10.1016/j.rpsm.2016.03.005.
74. Cohen D, Bogers JPAM, van Dijk D, Bakker B, Schulte PFJ. Beyond white blood cell monitoring: screening in the initial phase of clozapine therapy. J Clin Psychiatry. 2012;73:1307–12, http://dx.doi.org/10.4088/JCP.11r06977.
75. Bak M. Monitoring clozapine adverse effects calls for the integration of protocol and good clinical practice. J Clin Psychiatry. 2012;73:1313–4, http://dx.doi.org/10.4088/JCP.12com07964.
76. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-Year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009;374:620–7, http://dx.doi.org/10.1016/S0140-6736(09)60742-X.
77. Crump C, Ioannidis JPA, Sundquist K, Winkleby MA, Sundquist J. Mortality in persons with mental disorders is substantially overestimated using inpatient psychiatric diagnoses. J Psychiatr Res. 2013;47:1298–303, http://dx.doi.org/10.1016/j.jpsychires.2013.05.034.
78. Hayes RD, Downs J, Chang CK, Jackson RG, Shetty H, Broadbent M, et al. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. Schizophr Bull. 2015;41:644–55, http://dx.doi.org/10.1093/schbul/sbu120.
79. Kelly DL, Wehring HJ, Vyas G. Current status of clozapine in the United States. Shanghai Arch Psychiatry. 2012;24:110–3, http://dx.doi.org/10.3969/j.issn.1002-0829.2012.02.007.
80. Latimer E, Wynant W, Clark R, Malla A, Moodie E, Tamblyn R, et al. Underprescribing of clozapine and unexplained variation in use across hospitals and regions in the Canadian province of Québec. Clin Schizophr Relat Psychoses. 2013;7:33–41, http://dx.doi.org/10.3371/CSRP.LAWY.012513.
81. Gören JL, Meterko M, Williams S, Young GJ, Baker E, Chou CH, et al. Antipsychotic prescribing pathways, polypharmacy, and clozapine use in treatment of schizophrenia. Psychiatr Serv. 2013;64:527–33, http://dx.doi.org/10.1176/appi.ps.002022012.
82. Fayek M, Flowers C, Signorelli D, Simpson G. Underuse of evidence-based treatments in psychiatry. Psychiatr Serv. 2003;54:1453–4, http://dx.doi.org/10.1176/appi.ps.54.11.1453.
83. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. Psychiatr Serv. 2005;56:320–3, http://dx.doi.org/10.1176/appi.ps.56.3.320.
84. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. J Clin Psychiatry. 2003;64:30–4 [Internet].
85. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration – New York metropolitan region. Schizophr Bull. 2002;28:31–42.
86. Moore TA, Covell NH, Essock SM, Miller AL. Real-world antipsychotic treatment practices. Psychiatr Clin North Am. 2007;30:401–16, http://dx.doi.org/10.1016/j.psc.2007.04.008.
87. Joober R, Boksa P. Clozapine: a distinct, poorly understood and under-used molecule. J Psychiatry Neurosci. 2010;35:147–9, http://dx.doi.org/10.1503/jpn.100055.
88. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Geographic and clinical variation in clozapine use in the United States. Psychiatr Serv. 2014;65:186–92, http://dx.doi.org/10.1176/appi.ps.201300180.
89. Nielsen J, Røge R, Schjerning O, Sørensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. Eur Neuropsychopharmacol. 2012;22:818–24, http://dx.doi.org/10.1016/j.euroneuro.2012.03.003.
90. Xiang YT, Wang CY, Si TM, Lee EHM, He YL, Ungvari GS, et al. Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. Aust N Z J Psychiatry. 2011;45:968–75, http://dx.doi.org/10.3109/00048674.2011.607426.
91. Mortimer AM, Singh P, Shepherd CJ, Puthiryackal J. Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. Clin Schizophr Relat Psychoses. 2010;4:49–55, http://dx.doi.org/10.3371/CSRP.4.1.4.
92. Patel MX, Bishara D, Jayakumar S, Zalewska K, Shiers D, Crawford MJ, et al. Quality of prescribing for schizophrenia: evidence from a national audit in England and Wales. Eur Neuropsychopharmacol. 2014;24:499–509, http://dx.doi.org/10.1016/j.euroneuro.2014.01.014.
93. Grover S, Balachander S, Chakarabarti S, Avasthi A. Prescription practices and attitude of psychiatrists towards clozapine: a survey of psychiatrists from India. Asian J Psychiatr. 2015;18:57–65, http://dx.doi.org/10.1016/j.ajp.2015.09.013.
94. Bachmann CJ, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, et al. International trends in clozapine use: a study in 17 countries. Acta Psychiatr Scand. 2017:1–15, http://dx.doi.org/10.1111/acps.12742.
95. Olfson M, Gerhard T, Crystal S, Stroup TS. Clozapine for schizophrenia: state variation in evidence-based practice. Psychiatr Serv. 2016;67:152. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26522679 [Internet].
96. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014;14:102, http://dx.doi.org/10.1186/1471-244X-14-102.

97. Olfson M, Gerhard T, Crystal S, Stroup TS. Clozapine for schizophrenia: state variation in evidence-based practice. Psychiatr Serv. 2016;67:152, http://dx.doi.org/10.1176/appi.ps.201500324.
98. National Institute for Health and Care Excellence (NICE). Schizophrenia Clinical guideline [CG1]. https://www.nice.org.uk/guidance/cg1 [published date: December 2002; accessed 29.03.18].
99. Downs J, Zinkler M. Clozapine: national review of postcode prescribing. Psychiatr Bull. 2007;31:384–7, http://dx.doi.org/10.1192/pb.bp.106.013144.
100. Kreyenbuhl J, Buchanan RW, Dickerson FB, Dixon LB. The schizophrenia patient outcomes research team (PORT): updated treatment recommendations 2009. Schizophr Bull. 2010;36:94–103, http://dx.doi.org/10.1093/schbul/sbp130.
101. Mcilwain ME, Harrison J, Wheeler AJ, Russell BR. Pharmacotherapy for treatment-resistant. Neuropsychiatr Dis Treat. 2011;7:135–49, http://dx.doi.org/10.2147/NDT.S12769.
102. Stahl SM. Emerging guidelines for the use of antipsychotic polypharmacy. Rev Psiquiatr Salud Ment. 2013;6:97–100, http://dx.doi.org/10.1016/j.rpsm.2013.01.001.
103. Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. Ann Pharmacother. 2008;42:852–60, http://dx.doi.org/10.1345/aph.1K662.
104. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012;201:481–5, http://dx.doi.org/10.1192/bjp.bp.111.105833.
105. Royal College of Psychiatrists. Report of the Second Round of the National Audit of Schizophrenia (NAS); 2014. Available from: http://www.rcpsych.ac.uk/pdf/FINAL_report_for_the_second_round_of_the_National_Audit_of_Schizophrenia-8.10.14v2.pdf [accessed 29.03.18].
106. Tang C, Subramaniam M, Tat Ng B, Abdin E, Yin Poon L, Verma SK. Clozapine use in first-episode psychosis: the Singapore Early Psychosis Intervention Programme (EPIP) perspective. J Clin Psychiatry. 2016;77:e1447–53, http://dx.doi.org/10.4088/JCP.15m10063.
107. Trinczek E, Heinzel-Gutenbrunner M, Haberhausen M, Bachmann CJ. Time to initiation of clozapine treatment in children and adolescents with early-onset schizophrenia. Pharmacopsychiatry. 2016;49:254–9, http://dx.doi.org/10.1055/s-0042-116947.
108. Üçok A, Çikrikçili U, Karabulut S, Salaj A, Öztürk M, Tabak Ö, et al. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. Int Clin Psychopharmacol. 2015;30:290–5, http://dx.doi.org/10.1097/YIC.0000000000000086.
109. Mallinger JB, Fisher SG, Brown T, Lamberti JS. Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. Psychiatr Serv. 2006;57:133–6, http://dx.doi.org/10.1176/appi.ps.57.1.133.
110. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. Am J Psychiatry. 2003;160:1817–22, http://dx.doi.org/10.1176/appi.ajp.160.10.1817.
111. Kelly DL, Dixon LB, Kreyenbuhl JA, Medoff D, Lehman AF, Love RC, et al. Clozapine utilization and outcomes by race in a public mental health system: 1994–2000. J Clin Psychiatry. 2006;67:1404–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17017827
112. Manuel JI, Essock SM, Wu Y, Pangilinan M, Stroup S. Factors associated with initiation on clozapine and on other antipsychotics among Medicaid enrollees. Psychiatr Serv. 2012;63:1146–9, http://dx.doi.org/10.1176/appi.ps.201100435.
113. Iglesias García C, Iglesias Alonso A, Bobes J. Concentrations in plasma clozapine levels in schizophrenic and schizoaffective patients. Rev Psiquiatr Salud Ment. 2017;10:192–6, http://dx.doi.org/10.1016/j.rpsm.2017.06.002.
114. Bogers JPAM, Schulte PFJ, van Dijk D, Bakker B, Cohen D. Clozapine underutilization in the treatment of schizophrenia. How can clozapine prescription rates be improved? J Clin Psychopharmacol. 2016;36:109–11, http://dx.doi.org/10.1097/JCP.0000000000000478.
115. Simeone JC, Ward AJ, Rotella P, Collins J, Windisch R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990–2013: a systematic literature review. BMC Psychiatry. 2015;15:193, http://dx.doi.org/10.1186/s12888-015-0578-7.
116. Chen B, Fan VY, Chou Y-J, Kuo C-C. Costs of care at the end of life among elderly patients with chronic kidney disease: patterns and predictors in a nationwide cohort study. BMC Nephrol. 2017;18:36, http://dx.doi.org/10.1186/s12882-017-0456-2.
117. Roberts RM, Bartoces M, Thompson SE, Hicks LA. Antibiotic prescribing by general dentists in the United States, 2013. J Am Dent Assoc. 2017;148, http://dx.doi.org/10.1016/j.adaj.2016.11.020, 172–8.e1.
118. Sanz-Fuentenebro J, Vera I, Verdura E, Urretavizcaya M, Martínez-Amorós E, Soria V, et al. Pattern of electroconvulsive therapy use in Spain: proposals for an optimal practice and equitable access. Rev Psiquiatr Salud Ment. 2016, http://dx.doi.org/10.1016/j.rpsm.2015.12.003.
119. Xiang Y-T, Weng Y-Z, Leung C-M, Tang W-K, Ungvari GS. Clinical correlates of clozapine prescription for schizophrenia in China. Hum Psychopharmacol. 2007;22:17–25, http://dx.doi.org/10.1002/hup.821.
120. Si TM, Zhang YS, Shu L, Li KQ, Liu XH, Mei QY, et al. Use of clozapine for the treatment of schizophrenia: findings of the 2006 research on the China psychotropic prescription studies. Clin Psychopharmacol Neurosci. 2012;10:99–104, http://dx.doi.org/10.9758/cpn.2012.10.2.99.
121. Li Q, Xiang YT, Su YA, et al. Clozapine in schizophrenia and its association with treatment satisfaction and quality of life: findings of the three national surveys on use of psychotropic medications in China (2002–2012). Schizophr Res. 2015;168:523–9, http://dx.doi.org/10.1016/j.schres.2015.07.048.
122. Nielsen J, Young C, Ifteni P, Kishimoto T, Xiang YT, Schulte PFJ, et al. Worldwide differences in regulations of clozapine use. CNS Drugs. 2016;30:149–61, http://dx.doi.org/10.1007/s40263-016-0311-1.
123. Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. J Clin Psychiatry. 2011;72 Suppl. 1:4–8, http://dx.doi.org/10.4088/JCP.10075su1.01.
124. Alessi-Severini S, Biscontri RG, Collins DM, Kozyrskyj A, Sareen J, Enns MW. Utilization and costs of antipsychotic agents: a Canadian population-based study, 1996–2006. Psychiatr Serv. 2008;59:547–53, http://dx.doi.org/10.1176/ps.2008.59.5.547.
125. Pringsheim T, Lam D, Tano DS, Patten SB. The pharmacoepidemiology of antipsychotics for adults with schizophrenia in Canada, 2005 to 2009. Can J Psychiatry. 2011;56:630–4, http://dx.doi.org/10.1177/070674371105601009.
126. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. Pharmacoepidemiol Drug Saf. 2011;20:177–84, http://dx.doi.org/10.1002/pds.2082.
127. Trifirò G, Spina E, Brignoli O, Sessa E, Caputi AP, Mazzaglia G. Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the

years 1999–2002. Eur J Clin Pharmacol. 2005;61:47–53, http://dx.doi.org/10.1007/s00228-004-0868-3.
128. O'Brien A. Starting clozapine in the community: a UK perspective. CNS Drugs. 2004;18:845–52 [Internet].
129. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol. 2010;24:965–71, http://dx.doi.org/10.1177/0269881108100320.
130. Patel MX. Clinician hesitation prior to clozapine initiation: is it justifiable? Br J Psychiatry. 2012;201:425–7, http://dx.doi.org/10.1192/bjp.bp.112.114777.
131. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Ther Adv Psychopharmacol. 2015;5:88–96, http://dx.doi.org/10.1177/2045125314566808.
132. Carruthers J, Radigan M, Erlich MD, Gu G, Wang R, Frimpong EY, et al. An initiative to improve clozapine prescribing in New York State. Psychiatr Serv. 2016;67:369–71, http://dx.doi.org/10.1176/appi.ps.201500493.
133. Davis D, O'Brien MA, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? JAMA. 1999;282:867–74 [Internet].
134. Moreno EM, Moriana JA. Estrategias para la implementación de guías clínicas de trastornos comunes de salud mental. Rev Psiquiatr Salud Ment. 2016;9:51–62, http://dx.doi.org/10.1016/j.rpsm.2015.09.001.
135. Phanthunane P, Vos T, Whiteford H, Bertram M. Cost-effectiveness of pharmacological and psychosocial interventions for schizophrenia. Cost Eff Resour Alloc. 2011;9:6, http://dx.doi.org/10.1186/1478-7547-9-6.
136. Attard A, Taylor DM. Comparative effectiveness of atypical antipsychotics in schizophrenia: what have real-world trials taught us? CNS Drugs. 2012;26:491–508, http://dx.doi.org/10.2165/11632020-000000000-00000.
137. Williams T, Purvis TL. Development of an outpatient pharmacist-managed clozapine clinic. Am J Health Syst Pharm. 2012;69:1192–5, http://dx.doi.org/10.2146/ajhp110461.
138. Freudenreich O, Henderson DC, Sanders KM, Goff DC. Training in a clozapine clinic for psychiatry residents: a plea and suggestions for implementation. Acad Psychiatry. 2013;37:27–30, http://dx.doi.org/10.1176/appi.ap.11090159.