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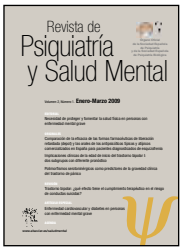

ORIGINAL

Comparing the efficacy of long-acting pharmaceutical forms (depot) versus oral forms of the atypical and conventional antipsychotics marketed in Spain for treating patients with schizophrenia

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Abstract

Introduction and objectives: Currently in Spain, 4 depot antipsychotics are available: flufenazine, pipotiazine, zuclopentixol and risperidone. The objectives of the present study are: *a)* to evaluate the efficacy of depot vs. oral forms of typical and atypical antipsychotics available in Spain for treating patients with schizophrenia; *b)* to compare the efficacy of different depot antipsychotics; *c)* to evaluate cost-effectiveness of typical and atypical depot and oral antipsychotics.
Methods: Systematic review of the literature between January 1980 and March 2007. Pharmaceutical companies of depot preparations were contacted aiming to include unpublished material.
Results: A total of 15 studies were included (13 journal manuscripts and 2 posters provided by the industry). Concordance between evaluators was moderate-high. The quality of selected studies was moderate-low. There were no differences in the efficacy between depot and oral risperidone. Efficacy of depot risperidone was higher than oral olanzapine (there were no differences regarding tolerability) and higher and better tolerated than oral zuclopentixol. The evidence was controversial when comparing the effi cacy of depot and oral flufenazine. There were no differences when comparing the efficacy between depot flufenazine and oral pimozide. Depot zuclopentixol was more effi cient than the oral preparation for treating patients with schizophrenia and violent behaviour. Finally, there were no differences regarding the effi cacy and tolerability between depot pipotiazine and depot flufenazine and between depot clopentixol and depot flufenazine.
Conclusions: There is few high-quality scientific evidence comparing depot and oral antipsychotics or different depot antipsychotics available in Spain. Selected evidence does not allow to conclude that depot antipsychotics are more effective and better tolerated than oral ones.

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PALABRAS CLAVE
Depot antipsychotics;
Antipsicóticos depot;
Antipsicóticos orales;
Esquizofrenia;
Revisión sistemática

Comparación de la eficacia de las formas farmacéuticas de liberación retardada (depot) y las orales de los antipsicóticos típicos y atípicos comercializados en España para pacientes diagnosticados de esquizofrenia

Resumen

Introducción y objetivos: Actualmente en España se comercializan 4 antipsicóticos depot: flufenazina, pipotiazina, zuclopentixol y risperidona. Los objetivos del presente estudio son: *a)* evaluar la eficacia de las formas depot y las orales de los antipsicóticos típicos y atípicos comercializados en España en pacientes diagnosticados de esquizofrenia; *b)* comparar la eficacia de los diferentes antipsicóticos depot, y *c)* evaluar el coste-efectividad de los antipsicóticos típicos y atípicos depot frente a los orales.

Métodos: Revisión sistemática de la evidencia entre enero de 1980 y marzo de 2007. También se contactó con las empresas farmacéuticas que comercializan las formas depot con el objetivo de incluir los trabajos aún no publicados.

Resultados: Se incluyeron 15 trabajos (13 artículos publicados y 2 póster facilitados por farmacéuticas). La concordancia entre evaluadores fue moderada-alta. La calidad de los trabajos fue moderada-baja. No hubo diferencias en la eficacia de la risperidona depot frente a la oral. La risperidona depot sería más eficaz que la olanzapina oral (pero no habría diferencias respecto de su tolerabilidad) y más eficaz y mejor tolerada que el zuclopentixol oral. La evidencia es contradictoria al comparar la eficacia de la flufenazina depot y la oral. No habría diferencias en la eficacia de flufenazina depot frente a pimozida oral. El zuclopentixol depot sería más efectivo que el oral en el tratamiento de los pacientes con esquizofrenia y conducta violenta. Finalmente, no se encuentran diferencias en la eficacia y la tolerabilidad de la pipotiazina depot y la flufenazina depot y entre clopentixol depot y flufenazina depot.

Conclusiones: Hay poca evidencia científica de calidad en que se comparen antipsicóticos depot y orales o diferentes antipsicóticos depot entre sí comercializados en España. La evidencia seleccionada no permite concluir que los antipsicóticos depot sean superiores a los orales en cuanto a eficacia y tolerabilidad.

Introduction

Schizophrenia is a serious mental illness that generates large economic costs due to its chronic nature and can have a great impact on the patient's personality and ability to adapt socially.[1-5] Approximately one person in every hundred will suffer schizophrenia over their lifetime, although the greatest incidence is observed in people around the age of 20.[6] Despite being many factors involved in its treatment, antipsychotic medication is undoubtedly a key element. Besides reducing the symptoms of the disorder, antipsychotics are also used as ongoing treatment aimed to avoid relapses.[7] Schizophrenic patients who do not take antipsychotics have a relapse rate of approximately 10% per month.[8,9] If this rate persists over time, total relapse is a fact after a year. On the other hand, the relapse rate in patients treated with antipsychotics is approximately 1.5% per month for inpatients and 3 to 4% per month for outpatients.[9] As the number of relapses and the non-treated periods increase, the prognosis worsens as do the long term results. Patients who suffer relapses do not recover their previous condition of social adjustment.[10]

Conventional delayed release antipsychotics (depot) were developed in the 1970s with the intention of improving long term treatment of schizophrenia. The main advantage of the depot presentations over oral antipsychotics is that they facilitate completion of the prescribed treatment.[11] Depot antipsychotics assure more predictable plasmatic concentrations of the active pharmaceutical ingredient, since variability associated with absorption and hepatic biotransformation are avoided.[12] The practitioner also has increased control of the handling of the antipsychotic and is therefore in a better position to adjust doses to reach optimum levels. Another advantage is that if the patient misses an injection, for whatever reason, there is no abrupt interruption. This makes a relapse less likely.[12] Among the disadvantages of depot antipsychotics is the pain in the injection area, the patient's rejection to puncturing and the feeling of being controlled.[13]

Despite the widespread acceptance that depot preparations favour the completion of treatment, the patient can still suffer relapses even when medication is assured by the injection. There is a discussion about which depot antipsychotic diminishes relapses and rehospitalisation the most, when compared with the oral antipsychotics.

Second generation or atypical antipsychotics were developed in the 1980s to offer a more effective and tolerable treatment to schizophrenic patients. These antipsychotics have proven to be at least just as effective as the conventional ones for the treatment of positive symptoms.[14] Some studies have also shown slight improvement in the negative symptoms and some recovery in cognitive aspects[15,16] which could reduce the chances of suicide[17] and of substance abuse.[18] Furthermore, it has been indicated that the atypical antipsychotics could help to stabilise mood, have sedative properties[19] and could protect against relapses in greater proportion to typical antipsychotics.[20] Comparatively, atypical antipsychotics are more expensive than the traditional ones.

At the late 1990s, the first atypical depot antipsychotic (risperidone) began development and to date, it has been established that it is just as effective as the oral preparation and well tolerated by schizophrenic patients.[21-23]

Four depot antipsychotics are currently being marketed in Spain: Modecate (active ingredient: fluphenazine), Lonseren (active ingredient: pipotiazine), Clopixol (active ingredient: zuclopenthixol) and Risperdal (active ingredient: risperidone).

The aims of the following systematic review are: *a)* evaluate the efficacy of the delayed release pharmaceutical types (depot) and the oral types of antipsychotics (typical and atypical) marketed in Spain for patients diagnosed with schizophrenia; *b)* compare the effectiveness of the different depot antipsychotics sold in Spain in patients diagnosed with schizophrenia, and *c)* appraise the cost-efficiency of the depot types versus the oral pharmaceutical forms of antipsychotics (typical and atypical) commercialised in Spain in patients diagnosed with schizophrenia.

Method

A systematic review of the literature available was carried out in the following data bases: MEDLINE (PubMed), PSYCINFO, ISI Web of Knowledge (with a transversal search in MEDLINE, Current Contents Connect, Web of Science, Zoological Records, BIOSIS Previews, Derwent Innovations Index, ISI Proceedings), Cochrane Plus Library (Cochrane Database of Systematic Reviews, Register of Randomised Clinical Trials, Health Technology Assessment Database [HTA] and NHS Economic Evaluation Database [NHS EED]) and Biological Sciences.

The pharmaceutical companies that market the depot forms in Spain were also contacted to review any unpublished papers.

All the literature published from January 1980 and March 2007 was reviewed. The search strategy was as follows: ("Phenothiazines" [MeSH] [Phenothiazine is a MeSH word that includes the active ingredient fluphenazine. Both terms were searched to assure that this active ingredient was included under both names] OR "pipothiazine" *[substance name]* OR Clopenthixol [MeSH] [Clopenthixol is the MeSH term of the active ingredient zuclopenthixol] OR "Fluphenazine" [MeSH] OR "Risperidone" [MeSH]) AND ("Randomized Controlled Trials" [MeSH]) AND ("Schizophrenia" [MeSH]) AND ("Delayed-Action Preparations" [MeSH] OR depot).

As a sensitivity analysis, the same search was performed, excluding the MESH term *randomized controlled trial* in order to avoid excluding articles which were randomised but did not include this term as MESH.

As a control measure, a second search was performed under the supervision of a documentalist from the financial entity, the Catalan Agency for Health Technology Assessment, (AATRM). This search strategy was applied only to the PubMed and PSYCINFO databases. After the search, there were no additional studies detected that had not been observed in the first.

Once the search was undertaken and after reading the titles and the abstracts, three researchers (AF, AP and CB) chose the relevant articles. For this review, the scientific evidence assessment was limited to those articles which:

1. Were randomised clinical trials or cost-efficiency reviews.
2. Compared a depot pharmaceutical format sold in Spain with any other typical or atypical oral antipsychotic medication.
3. Included the comparison between different depot medications sold in Spain. Therefore, articles that, for example, compared any of the four active ingredients marketed in Spain with the active ingredient haloperidol in its depot form or with fluphenthixol or perphenazine were excluded since none of these is approved by the Spanish Agency of Medicine and Healthcare Products (AEMPS).
4. Were written in English, French, Spanish, Italian or Portuguese.
5. Took into account trials on adult patients.
6. Contemplated some of the following result gauges: use of services (hospitalisations, emergency visits), improvement of the symptoms (evaluated through validated PANSS or GCI surveys) or of economic costs. Studies that evaluated the quality of life, therapeutic completion or adverse effects as main assessment criteria were also taken into consideration.

As a control measure in the search, the references included in the systematic reviews collected in the Cochrane database were checked manually.

The selected articles were masked (the journal name, authors, institutions and any other identifying features were removed) and sent to three experts in methodology and schizophrenia (JMH, VP, JB) who independently evaluated the quality of the articles using the Jadad three-point scale.[24] The points were listed with a description of the randomised assignation (rated with 2 points), double-blind (2 points) and data inclusion of treatment abandonment and discontinued monitoring (1 point).

Besides assessing the quality of the articles, the reviewers also gathered other data from the articles using a list drawn up by the research team aimed at increasing objectivity, reliability and accuracy. The list included the following:

- Article reference (number assigned for its identification, as it was masked).
- Design type.
- Sample.
- Average age.
- Sex (%).
- Sample size.
- Active ingredient, administration method and individual dosage of each one.
- Result measurement.
- Monitoring period.
- Results (with variability and statistical significance indicators).
- Jadad quality evaluation scale.
- Remarks.

Each expert reviewer received the material together with a completed example. Consensus was met in the event of discrepancies between the experts.

Results

The first PubMed search (including the MeSH term *randomized controlled trial*) returned 11 articles. When this MeSH term was excluded, the search returned 135 matches. Searches in PSYCINFO resulted in 190 documents. Searches in the Cochrane Library returned 130 documents among systematic reviews, clinical trials and economic appraisals. The search in the ISI Web of Knowledge recovered 175 documents. The Biological Sciences search did not return any relevant findings. Finally, the pharmaceutical companies consulted furnished us with 21 studies presented at congresses that had not been published to date.

The total number of documents detected was 651. After excluding duplicates from the databases and eliminating studies which, from the title or the abstract, did not comply with the inclusion criteria, a total of 34 documents were selected that clearly complied with all of the criteria needed or that required a review of the full text to decide

TABLE 1 **Selected studies and assessment of their quality**

Author (year)	Format	Score on the Jadad scale (0-5))
Depot versus oral risperidone		
Bai et al[26] (2006)	Article	3
Bai et al[27] (2006)	Poster study	2
Chue et al[28] (2004)	Article	4
Depot risperidone versus oral olanzapine		
Rabinowitz et al[29] (2006)	Poster study	1
Depot versus oral fluphenazine		
Levine et al[30] (1980)	Article	3
Schooler et al[31] (1980)	Article	4
Depot fluphenazine versus oral pimozide		
McCreadie et al[33] (1982)	Article	4
McCreadie et al[32] (1980)	Article	4
Depot versus oral zuclopenthixol		
Arango et al[25] (2006)	Article	2
Depot versus depot		
Rubio et al[34] (2006)	Article. Compares depot zuclopenthixol with depot risperidone	3
Leong et al[35] (1989)	Article. Compares depot pipotiazine with depot fluphenazine	2
Albert et al[36] (1980)	Article. Compares depot pipotiazine with depot fluphenazine	3
Walker[37] (1983)	Article. Compares depot clopenthixol* with depot fluphenazine	3
Cost-efficiency studies		
De Graeve et al[38] (2005)	Article. Compares depot risperidone with oral olanzapine and depot haloperidol	–
Yang et al[39] (2005)	Article. Compares depot risperidone with oral olanzapine and depot haloperidol	–

*Clopenthixol is a synonym of zuclopenthixol.

whether they met the requirements or not. These 34 studies were sent to the independent expert reviewers.

Of the 34 preselected studies, 15 were included in this review since they met the inclusion criteria (clinical trials or cost-efficiency studies and the comparisons contemplated active ingredients and administration methods commercialised in Spain). Of these 15 studies, 13 were articles published in scientific journals and 2 were papers provided by pharmaceutical companies presented at scientific congresses that had not yet been published. Of the 13 articles, 11 were randomised clinical trials and 2 were cost-efficiency studies. Table 1 summarises the selected studies and the quality assessment.

Quality of the selected studies

Concordance between the expert reviewers resulted moderately-high; 12 out of 13 clinical trials were evaluated by 3 experts (the article by Arango et al[25] was rated by only one as it was included after the shipping of the documents to the other experts). Out of the 12 evaluated by everyone, 7 obtained the same score on the Jadad scale.

Of the 13 clinical trials, 9 exceeded or equalled the minimum quality score (3 points). The 2 cost-efficiency studies were based on panels of experts and systematic review of the literature.

Studies comparing depot and oral presentations

Table 2 summarises the detailed evidence collected by the different studies comparing depot and oral antipsychotics.

Depot versus oral risperidone

Three studies compare depot and oral risperidone. One was a poster. The first study, by Bai et al,[26] compared 49 inpatients with a diagnosis of schizophrenia according to the DSM-IV criteria that were randomised in both presentations of risperidone and monitored for 12 weeks. The measure of results is a reduction in symptoms (efficiency) and adverse effects (safety) as well as improved quality of life (tolerability). The authors' conclusions are that, comparing the measurements at the start and end of the follow-up, depot risperidone is safer since it reduces the adverse effects evaluated on the Udvalg for Kliniske Undergolser scale (UKU) (—2.12 ± 3.46 versus —0.13 ± 2.17; p = 0.037). The group taking depot risperidone also showed a reduction in prolactin concentrations at 4 weeks (—13.4 ± 24.5 versus 6.7 ± 27.9ng/ml; p = 0.009) and 12 weeks (—19.3 ± 19.1 versus 3.1 ± 26.6ng/ml; p = 0.001). Patients taking depot risperidone presented significant changes in the social functioning items of the SF-36 survey and increased their scores (7.5 ± 20.1 versus —11 ± 31.1; p = 0.017). No changes were detected in the remaining SF-36 items. In relation to efficiency, patients taking depot risperidone presented deterioration in the positive symptoms evaluated with the Positive and Negative Syndrome Scale (PANSS) (0.72 ± 3.52 versus —1.24 ± 3.81; p = 0.022). No other differences were noted in the remaining scales.

The second study, by Bai et al[27] was carried out with 45 inpatients with a diagnosis of schizophrenia and monitored for 48 weeks. The working procedure is as described above. These data, presented in the shape of a poster, show that the depot risperidone continues displaying a reduction in adverse effects evaluated with the UKU (—2.3 versus —0.6; p = 0.002) as well as of the prolactin concentrations (—17.4 versus 8.8; p < 0.001). By the same token, after 48 weeks of monitoring, the group taking depot risperidone displayed a worsening of the positive symptomatology evaluated with the PANSS (0.1 versus —1.4; p = 0.039).

The study by Chue et al[28] included 640 patients with schizophrenia who, after being stabilised with oral risperidone, were randomised with the oral or depot presentations. The result measurements used evaluated the symptomatology (efficiency) and the adverse effects (safety). It was designed as a non-inferiority trial, in which the aim was to find no differences between the groups. No differences were found between the groups; both displayed an improvement with respect to the baseline measurement. The authors conclude that the change can be made from oral to depot risperidone since there are no differences in efficiency and tolerance. Furthermore, the pain caused by the injection is perceived as low (18-20 out of 100 on an analogical scale).

Depot risperidone versus oral olanzapine

The study by Rabinowitz et al,[29] presented as a poster, is a non-inferiority design in which 618 patients diagnosed with schizophrenia or schizoaffective disorder taking oral olanzapine were randomised with this treatment or depot risperidone. The result measurements included symptomatology (efficiency) and adverse effects (tolerability). The authors conclude after 12 months that there were more patients in the depot risperidone group displaying a > 20% reduction in symptomatology evaluated with the PANSS (*odds ratio* [OR] = 2.36; 95% confidence interval [CI], 1.63-3.43). This tendency was maintained until the end of the study (week 53) (OR = 1.46; 95% CI, 1.09-1.95). No significant differences were detected in respect to adverse effects. The authors concluded that the depot risperidone was not inferior to the oral olanzapine in the short term.

Depot fluphenazine versus oral fluphenazine

The study by Levine et al[30] is an article that evaluates 67 patients with schizophrenia in which the discontinuation of treatment and its continuation with the oral format or a placebo are compared. The result measurements are relapses (efficiency) and adverse effects (tolerability). The authors conclude that the relapses are more frequent in the group that discontinues treatment than in the group continuing treatment. On comparing the groups that continue treatment (n = 27), the depot group relapsed less than the one that was on oral medication (67.65 versus 81.81%). The group taking depot fluphenazine presented less proportion of involuntary movements than the group taking oral fluphenazine.

The Schooler et al[31] study is an article which studies 214 randomised participants after a period with oral fluphenazine, with oral or depot fluphenazine. The result measurements

TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain**

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
Depot versus oral risperidone	Bai et al[26] (2006a)	Randomised clinical trial. Blind tester After 3 months of stabilisation of the disorder with oral risperidone, patients were randomly grouped as continuing oral treatment or changing to a depot. Followed-up for 12 weeks.	50 participants; 25 oral risperidone (52% males; aged 48.1 ± 14.1); 25 depot risperidone (48% males; aged 44.7 ± 9.2)	Stabilised inpatients diagnosed with schizophrenia according to DSM-IV	Oral risperidone: the original dose is maintained. Depot risperidone: A dose equivalent to the one they were on (25, 37.5 or 50mg) is administered every fortnight.)	One participant abandons the depot risperidone group due to stomach pain.I	Total PANSS: Differences before-after. Oral risperidone, —2.4 ± 10.4. Depot risperidone, —0.16 ± 9.04). No differences. Differences only on the positive scale. In the depot risperidone group, it increased by 0.72 ± 3.52 points, statistically significantly larger than the change in the oral group (—1.24 ± 3.8; p = 0,022). No differences in the change in depot and oral evaluated by GAF and CGI.	UKU: Difference before-after. The depot risperidone group (—2.12 ± 3.46) decreases more than the oral risperidone (—0.13 ± 2.17; p = 0.037). The concentrations of prolactin are also lowered in the depot group in weeks 4 and 12 (—13.4 ± 24.5 versus 6.7 ± 27.9ng/ml; p = 0.009, y —19.3 ± 19.1 versus 3.1±26.6ng/ml; p = 0.001). AIMS: NS. BARN: NS.ESP: NS	—	Evaluated with the SF-36 scale. The depot group shows an improvement in the social function domain. Authors do not reveal the data.
Depot versus oral risperidone	Bai et al[27] (2006). Poster	Randomised clinical trial. Blind tester After 3 months of stabilisation of the disorder with oral risperidone, patients were	50 participants; 25 oral risperidone (52% males; ages, 48.1 ± 14.1); 25 depot risperidone	Stabilised hospital patients diagnosed with schizophrenia according to the DSM-IV	Oral risperidone: the original dose is maintained. Depot risperidone: a dose equivalent to	5 participants abandon. All from the depot risperidone group: 2 due to Worsening	Group on depot risperidone increases points on the positive PANSS scale (0.1 versus —1.4; p = 0.039). No further results are given	UKU: the depot group reduces the point total (—2.3 versus —0.6; p = 0.002). The depot group presents lower prolactin concentrations		

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TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
		randomly grouped as continuing oral treatment or changing to a depot. Followed-up for 48 weeks (second part of the previous article)	(48% males; 44.7 ± 9.2)	the one they were on (25, 37.5 or 50mg) is administered every fortnight.	of the symptoms, 2 due to adverse effects and 1 withdrew consent			(—17.4 versus 8.8; p < 0.001). No further results given.		
Depot versus oral risperidone	Chue et al[28] (2004)	Randomised clinical trial. Double-blind, multicentred. Non-inferiority (the sample size is calculated with a potential of 90%). After an 8-week period of stabilisation with oral risperidone, they are randomised to depot or oral. 12 week follow-up	642 randomised. 2 participants are abandon before starting the study; 321 with oral risperidone (63% male; ages 39.9 ± 0.6); 319 with depot risperidone (65.6% male; aged 40.1 ± 0.6)	Schizophrenia diagnosis according to DSM-IV. PANSS > 49. Normal biochemical values	Oral risperidone group: same dose as before + placebo injection every fortnight. Depot risperidone group: daily oral placebo dose + injection of 25, 50 or 75mg every fortnight.	From the oral group, 271 finalised (84%); 4.7% did not continue due to adverse effects; 4% did not consent to treatment. Inadequate response: 2.5%. 256 finished in the depot risperidone group (80%). 5.6% did not finish due to adverse effects. 5.3% did not give	Total PANSS: differences before-after. Oral risperidone: —6.3 ± 0.7; p<0.001. Depot risperidone: —5.4 ± 0.7; p <0.001. Comparison (95% CI, —0.9 to 2.78): superior interval not over 6. No differences. CGI: before-after. Oral risperidone: the rate of slightly ill patients evaluated passes from 46.9 to 57.8%. Depot risperidone: the rate of slightly ill patients evaluated passes	In the oral risperidone group: 59.9% inform of adverse effects, with depot risperidone, 61.1%. No changes in biochemical measurements or weight gain. No differences in the ESRS scoring (data unavailable). Both groups present reference and final elevated prolactin concentrations. Only a significant lowering of		

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TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
						consent. Inadequate response: 3.8%	from 49.2 to 57.9%	the values are found in the depot risperidone group, but this is not considered significant from a clinical viewpoint. There are no differences in pain perception		
Depot versus oral olanzapine	Rabinovitz et al[28] (2006). Poster	Randomised clinical trial. No masking notice. No inferiority design but there is no reflection about beta error or statistic power. 53 week follow-up	618 participants. Information to only those taking olanzapine and oral risperidone and being randomised to continue using olanzapine or or depot risperidone	Schizophrenia or schizo-affective diagnosis	Oral olanzapine group: daily 5-20mg. Depot risperidone group: 25-50mg every fortnight	Not specified.	Patients in depot Risperidone group got better PANSS (>20% reduction) at 1 month, 12 weeks (OR = 2.36; 95% CI,1.63-3.43) and 53 weeks (OR = 1.46; 95% CI, 1.09-1.95). Better PANSS, hostile and thought disorder factors. No more results	No difference in extrapyramidal effects. Patients from the olanzapine group gained weight. No more results		

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TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
Depot versus oral fluphenazine	Levine et al[30] (1980)	Double-blind random clinical trial. The main variable is the continuation or discontinuation of treatment and the second is type of medication: depot or oral	67 participants are random to continue or discontinue medication. Of the 67 participants, 33 took oral fluphenazine and 34 depot fluphenazine. Among the oral intakes, 82% (n = 23) discontinued medication, while those in the depot group 68% (n = 27) discontinued	Diagnosis of schizophrenia (continuation of a 1979 study)	Oral fluphenazine group: 24mg/day. Depot fluphenazine group: 30.9mg/3 weeks	—	—	AIMS: the group that discontinues presents adverse effects. The group that continues with oral fluphenazine presents more adverse effects than the one that continues with the depot	The group that discontinues relapses more than the one that continues. The group taking oral fluphenazine (33% of 6 participants) relapses more than the group taking depot fluphenazine (18% out of 11 participants)	
Depot versus oral fluphenazine	Schooler et al[31] (1980)		Double-blind random clinical trial. 1 year follow-up. Multicentric. Patients were stabilised with oral fluphenazine for a week; then randomised	290 patients: 147 oral fluphenazine group; 143 depot fluphenazine group	New inpatients, aged 18-55; diagnosis of schizophrenia undertaken by 2 psychiatrists; with a minimal score of moderate in the BPRS scale	Oral fluphenazine group: Placebo injection every 3 weeks and an oral dose (2.5 to 60mg/day). Depot fluphenazine group: daily oral placebo + injection every	76 were excluded from the study during the intensive stage. 214 finally entered the maintenance stage	No differences in symptomatology	No differences in the rehospitalisations (35% of the oral group versus 26% of the depot group)	

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TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
						3 weeks (12.5 to 100mg). Fluphenazine group.				
Depot fluphenazine versus pimozide	Mc Creadie et al[33] (1982)	Double-blind random clinical trial. Follow-up for 9 months	29 male inpatients: 14 with oral pimozide; 15 with depot fluphenazine	Be in good health. Meet the Feighner requirements for schizophrenia diagnosis. Be stabilised according to the criteria of the physician and nursing staff. Sign the consent	Depot fluphenazine group: Depot doses equivalent to those taking + placebo pills. Oral pimozide group: Placebo injections + oral pimozide. The oral drug (placebo or active) is administered daily for a week, 4 days during the following, twice in the third and once in the fourth	1 participant is excluded before starting without stating the reason. Of the 28 remaining: 5 out of 13 abandon the pimozide group; 6 out of 15 abandon the depot fluphenazine group	Mental state: Hamilton-Lorr Scale: no differences. Depression and anxiety: Krawiecka Scale: no differences. Wing Ward Behaviour Scale: no differences.	More dyskinesias (evaluated by physicians) in the pimozide group ($p < 0.05$). The patients in the pimozide group lost more weight than those in the depot fluphenazine Group ($p < 0.008$). No differences in prolactin concentrations		
Depot fluphenazine versus pimozide	Mc Creadie et al[32] (1980)	Double-blind random clinical trial. Follow-up for 9 months	35 patients (9 inpatients and 26 day hospital outpatients): 17 with oral pimozide and 18 with depot fluphenazine	Be in good health. Meet the Feighner requirements for schizophrenia diagnosis. Be stabilised	Depot fluphenazine group (12.5mg): Once a week+oral placebo. Pimozide group: 9mg/4 days per	1 participant in the pimozide group was excluded due to rejection to medication	3/16 in the pimozide group and 3/18 in the depot fluphenazine group had relapses in the positive	Pimozide group: before treatment, only 1 participant was taking anti-parkinsonians and by the end, 8 ($p < 0.02$).		

(Continues on the following page)

TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
				according to the criteria of the physician and nursing staff. Sign the consent	week+placebo injection		symptomatology (assessed by physicians). Mental state: Hamilton-Lorr Scale: no data. Depression and anxiety: Krawiecka Scale: no data. Wing Ward Behaviour Scale: both groups worsened in relation to pre-treatment. No differences	Depot fluphenazine group: before treatment, 5 were taking anti-parkinsonians; then, 6 (no differences)		
Depot versus oral zuclopenthixol	Arango et al[25] (2006)	Randomised clinical trial. Blind-tested. One year follow-up	46 participants met the criteria and were randomised to oral or depot; 38/46 males (20, oral and 26 depot)	DSMIV diagnostic criteria or schizophrenia. At least one violent episode with a score of n > 3 in physical aggression on the MOAS subscale. Presence of a family member willing to participate in the research and living with the patient. Informed consent	Depot zuclopenthixol group: flexible dose once a fortnight. Oral zuclopenthixol group: daily flexibility. Participants take Biperidol (oral or injectable). Oral placebo benzodiaze-pines are permitted	The article mentions that 5 out of 46 abandon, but n = 46 is still shown. No differences in the abandon rate or between the two groups (2 from depot and 3 from oral)	8/20 in the oral and 12/26 in the depot had a violent episode in the follow-up (NS) 12/2/6 in the oral and 14/6/6 in the depot were evaluated as not-applicable/ moderate/ severe episodes, respectively (NS). Among the violent patients (MOAS > depot there were 2 during follow-up: oral, n = 8 and depot, n = 12), the oral group had on average more		10/26 in the depot group and 6/20 in the oral group were hospitalised (p = 0.55; w/o differences)	

(Continues on the following page)

TABLE 2 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient dose	Abandonment	Symptomatology	Adverse effects	Use of services	Quality of life
							episodes per month: 1.63 ± 1.46 versus 0.44 ± 0.3; p = 0.034. Patients in the depot group took longer to have the first violent episode: 2.38 ± 1.73 versus 4.71 ± 1.73 months (p = 0.012), and they complied better with treatment: 6.2 ± 3.11 versus 8.62 ± 3.43 months (p = 0.011). No differences in the PANSS			

were adverse effects (tolerability) and the probability of relapse (efficiency). The authors concluded that there were no differences in these two result measurements.

Depot fluphenazine versus oral pimozide

In the first study by McCreadie et al,[32] 35 males taking depot fluphenazine or oral pimozide treatment were compared. To assure the double-blind testing, the patients taking oral pimozide received a placebo injection and the depot fluphenazine group was administered a placebo pill. The result measurements were patient mental state (efficiency), prosocial behaviour (efficiency) and adverse effects (tolerability). The authors concluded that no differences were observed between the two groups in the relapse proportion. On performing intragroup comparisons, it was observed that the patients taking oral pimozide required an antiparkinsonian drug (1 compared with 8; $p < 0.02$). This change was not observed in the depot fluphenazine group (5 compared with 6). No changes were detected in prosocial behaviour.

In the second McCreadie study,[33] the comparison was between 29 males previously stabilised with antipsychotics then later randomised with intermittent pimozide doses or depot fluphenazine. To assure the double-blind testing, the patients taking oral pimozide received a placebo injection and the depot fluphenazine group was administered a placebo pill. The result measurements were mental state, adverse effects and relapses. Authors observed no relapse differences between the groups. Nevertheless, the group taking oral pimozide presented an increase in dyskinesia ($p < 0.05$) and greater weight loss ($p < 0.05$).

Depot zuclopenthixol versus oral zuclopenthixol

The Arango et al[25] study was carried out on 46 schizophrenic patients with a prior history of violence, randomised to treatment with oral or depot zuclopenthixol. The result measurement was the reduction in violent episodes as informed by a family member that filled out a daily register of the patient's violent behaviour. Violence was also evaluated with the Modified Overt Aggression Scale (MOAS). Other result measurements were symptomatology (efficiency) and adverse effects (tolerability). Authors concluded that no differences were observed in symptomatology and violent episodes (severity and frequency). Although differences were observed in favour of the group receiving depot zuclopenthixol, in the subgroup with > 2 points on the MOAS physical aggression subscale. In this subgroup, those receiving depot zuclopenthixol experienced a lower average of violent monthly episodes than those taking oral zuclopenthixol (0.44 ± 0.3 versus 1.63 ± 1.46; $p = 0.034$). In the full sample, differences were observed in favour of those receiving depot zuclopenthixol in the number of months since the start of the study to the first violent episode (4.71 ± 1.73 versus 2.83 ± 1.75; $p = 0.012$) and in the number of months of therapy (8.62 ± 3.43 versus 6.2 ± 3.11; $p = 0.011$). Regarding efficiency, no differences were observed between the groups in the PANSS positive symptoms subscale. The authors do not mention data from other subscales. Respecting tolerance, the authors only describe the percentage of participants in both groups that were hospitalised and the number of hospitalisations. No differences were detected between the groups in these measurements ($p = 0.55$ and $p = 0.98$ respectively).

Comparison between depot forms

In table 3, the evidence of the four studies comparing two depot drugs is summarised. These met the selection criteria (randomised clinical trial and sold in Spain).

Rubio et al[34] presented the results of a study that evaluated the efficiency of depot risperidone compared to depot zuclopenthixol in a total of 115 schizophrenic participants with co-morbid substance abuse. The main result measurement was the presence of substances in the urine and a survey of complications caused by substance abuse. Other result measurements were symptomatology (efficiency) and adverse effects (tolerability). All of the subjects also received psychological treatment. The authors concluded that the participants in the risperidone group presented less positive urine tests than those in the zuclopenthixol group (8.67 ± 3 versus 10.36 ± 3.1; $p = 0.005$), a greater improvement in the PANSS negative symptomatology subscale (18.80 ± 8.71 versus 23.81 ± 4.7; $p = 0.008$), in the general subscale (32.02 ± 9.71 versus 37.62 ± 11.82; $p = 0.05$) and in the total subscale (64.93 ± 19.9 versus 74.03 ± 20.9; $p = 0.02$). Furthermore, 89% of those receiving risperidone versus 50% of those administered with zuclopenthixol presented a 20% decrease in the PANSS scale ($p < 0.0001$). That is, the depot risperidone displayed greater efficacy in the reduction of symptoms than the depot zuclopenthixol.

The group taking risperidone also displayed less adverse effects assessed with the UKU scale ($p = 0.04$) and required less antiparkinsonian drugs ($p < 0.01$). Moreover, patients receiving risperidone complied more with psychological treatment; they attended an average of 19.7 ± 2.83 sessions versus 17.6 ± 3.9 in the zuclopenthixol group ($p = 0.001$). The total number of sessions was foreseen to be 24. On the other hand, 92.9% of the risperidone group attended more than 75% of the sessions versus an attendance of 67.8% of the zuclopenthixol group ($p = 0.001$).

The Leong et al[35] study compared pipothiazine with fluphenazine (both depot) administered to a sample of 60 patients, randomly assigned to the treatment, suffering schizophrenia according to the International Classification of Diseases (ICD). The result measurements were symptomatology (efficiency) and adverse effects (tolerability). The authors found no significant differences between the groups.

Albert et al[36] undertook a study of 33 male inpatients with schizophrenia and stabilised with chlorpromazine over two months and then randomised with pipothiazine or fluphenazine (both depot). The result measurements were symptomatology (efficiency) and adverse effects (tolerability). The authors found no differences in general symptomatology assessed with the Brief Psychiatric Rating Scale (BPRS), the Nurses Observation Scale for Inpatient Evaluation (NOSIE) and the Clinical Global Impression (CGI). Despite these conclusions, the group receiving pipothiazine displayed a greater tendency to improvement. Neither there

TABLE 3 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain**

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient doses	Abandonment	Symptomatology	dverse effects	Use of services	Quality of life
Depot zuclopenthixol versus depot risperidone	Rubio et al[34] (2006)	Randomised clinical trial. Not blind to avoid complications. Evaluators are blind. Monitoring for 6 months. Assessed fortnightly	115 inpatient participants randomised to one of the two conditions. 7 to 15 days later, they are discharged and undergo outpatient monitoring (57 with depot risperidone and 58 with depot zuclopen-thixol)	Schizo-phrenia diagnosis with comorbidity of substance abuse other than caffeine or nicotine. Age, 18-65 years	Not reported. All the participants included also followed a 24-week structured psychotherapy program for the treatment of substance abuse	6/58 from the zuclopen-thixol group and 3/57 from the risperidone group abandoned the study. Of the 9 that abandoned, 5 due to worsening of the symptoma-tology and the other 4 did not follow the psychothera-peutic sessions	The depot risperidone group obtained less positive testing of substance abuse in the urine: 8.67 ± 3 versus 10.36 ± 3.1 ($p = 0.005$). At 6 months, the depot risperidone group scored lower in the negative PANSS: 18.8 ± 8.71 versus 23.81 ± 7.4 ($p = 0.008$) on the total PANSS: 64.93 ± 19.9 versus 74.03 ± 20.9 ($p = 0.02$). No differences were detected in the positive PANSS or the general PANSS	ESRS: no differences between the groups at 6 months. UKU: differences favour the depot risperidone group in lower the score ($p<0.04$). No further results provided	The depot risperidone group obtains a higher attendance average to the psychotherapy sessions: 19.7 ± 2.83 versus 17.61 ± 3.9 ($p = 0.001$). Moreover, 92.91% of the group taking depot risperidone versus 67.79% taking zuclopenthixol attend more than 75% of the sessions ($p = 0.001$)	
Depot pipotiazine versus depot fluphenazinet	Levine et al[35] (1989)	Randomised clinical trial. Evaluators are blind. Monitoring for 28 weeks	60 patients are randomised to receive depot pipotiazine or depot fluphenazine (30/30); 27/60 males. Average age of 37.8 ± 1.87	Requiring medication to maintain the remission of schizophrenia diagnosis	Pipotiazine palmitate: 25-50mg every 4 weeks Fluphenazine decanoate: 12.5-50mg every 4 weeks	Only one participant in the pipotiazine depot group abandoned	BPRS: pipotiazine group: 13 improved versus 5 in the fluphenazine group; 10 did not vary versus 17 in the fluphenazine group; 6 worsened in each group;	No differences detected in the adverse effects: 13/30 in the pipotiazine group versus 12/30 improve; 8/30 versus 9/30 invariable; 8/30 versus 8/30 worsen		

(Continues on the following page)

TABLE 3 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient doses	Abandonment	Symptomatology	dverse effects	Use of services	Quality of life
			Patients in schizophrenia remission, according to the ICD				no information provided on 2 in the fluphenazine group. No differences detected ($p > 0.05$). CGI also detected no differences ($p > 0.05$). No differences in severity either	($p > 0.05$). No changes are detected in akinesia ($p > 0.05$), akathisia ($p > 0.05$), Parkinson's ($p > 0.05$) and dystonia ($p > 0.05$)		
Depot pipotiazine versus depot fluphenazine	Albert et al[36] (1980	Randomised clinical trial, double-blind; 39 weeks monitoring	33 male inpatients: 11 with 100mg depot pipotiazine; 11 with 150mg depot pipotiazine; 11 with 50mg depot fluphenazine	Chronic schizophrenia. No more criteria expressed	Depot pipotiazine: 100mg; depot pipotiazine: 150mg; depot fluphenazine: 50mg. Monthly injections	Not expressed	Total BPRS score: the improvement in the 100mg depot pipotiazine group was 19.7%. The improvement in the 150mg depot pipotiazine group was 16.9%. The depot fluphenazine improved 7.2% after 39 weeks. Insignificant tendency ($p < 0.11$) in the last month reduction, although there was in the first month. NOSIE: in the psychosis and irritability factor, there	There are no differences between the three groups in the frequency of extrapyramidal symptoms. Tendency to more symptoms in the 150mg pipotiazine group. Not significant		

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TABLE 3 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient doses	Abandonment	Symptomatology	dverse effects	Use of services	Quality of life
							is favourable improvement with pipotiazine in the last month ($p < 0.05$). CGI: greater tendency to improve over the last month in the pipotiazine groups than in the fluphenazine group ($p < 0.1$)			
Depot c lopenthixol versus depot fluphenazine	Walker[37] (1983)	Randomised clinical trial, double-blind; 24 weeks monitoring preceded by 12 open weeks in which dose is adjusted	Of the 45 participants living in the community, 6 abandoned. The sample was of 39 (19, clopenthixol; 20, fluphenazine)	Chronic schizophrenia. No criteria mentioned	Clopenthixol: 100mg/month to 400mg/fortnightly. Fluphenazine 12.5mg/month to 37.5mg every 3 weeks	6 abandoned (loss of follow-up); total: 39 participants	CGI: improvement in the clopenthixol group scores (4.1 to 3.2) after 24 weeks of monitoring ($p < 0.05$). The fluphenazine group went from 3.5 to 3 (insignificant differences). BPRS: improvement in the clopenthixol group scores (14.3 to 11.1) after 24 weeks of monitoring ($p < 0.05$).	No differences detected in the adverse effects	2/19 from the clopenthixol group versus 3/20 from the fluphenazine group are hospitalised during the monitoring stage	

(Continues on the following page)

TABLE 3 **Evidence table. Depot antipsychotics versus oral antipsychotics marketed in Spain** *(Continuation)*

						Results				
Active ingredient	Author (year)	Design	Sample size	Inclusion criteria	Active ingredient doses	Abandonment	Symptomatology	dverse effects	Use of services	Quality of life
							The fluphenazine group went from 11.7 to 9.1 (insignificant differences). Krawiecka, Goldberg and Vaughan Scale: improvement in the clopenthixol group scores (6.8 to 5.7) after 24 weeks of monitoring (NS). The fluphenazine group passed from 5.3 to 3.8 ($p < 0.05$)			

were any differences found between the groups in presence of secondary symptoms evaluated with the Extrapyramidal Evaluation Scale and analysis.

Finally, the Walker[37] study compared depot clopenthixol with depot fluphenazine in a sample of 45 patients diagnosed with chronic schizophrenia monitored for 24 weeks under randomised treatment. The result measurements were symptomatology (efficiency) and adverse effects (tolerability). The authors found no differences between these groups.

Pharmaco-economic studies

Table 4 summarises evidence from the two selected cost-efficiency studies which assessed the cost-efficiency of the depot risperidone versus other oral and depot drugs.

De Graeve et al[38] performed a cost-effectiveness study comparing depot risperidone, oral olanzapine and depot haloperidol from the Belgian health system perspective over a period of 2 years. The authors concluded that the depot risperidone was more cost-efficient than the other two drugs.

Lastly, Yang et al[39] studied how the use of depot risperidone versus oral olanzapine and depot haloperidol improved completion and, as a consequence, the efficacy and cost-efficiency of the drug. The authors concluded that the depot risperidone is more cost-efficient than the oral olanzapine and the depot haloperidol in treating schizophrenia in the group of patients with stabilised disorder. The diagnosis evolved over 1 to 5 years. It is of importance to note that a possible conflict of interests was detected, given that one of the experts participating in the study worked for the pharmaceutical company manufacturing the depot risperidone.

Summary of the Cochrane collaboration systematic review conclusions

As a control measure, four meta-analyses from the Cochrane collaboration were selected. These contemplated the four active ingredients targeted in this review in their depot format.

The review by David et al[40]: "Depot fluphenazine decanoate and enanthate for schizophrenia" (2004) compared any of these two with the placebo and another with a depot or oral antipsychotic. Furthermore, they compared different doses of depot fluphenazine. Insofar as the conclusions of the depot-oral and depot-depot comparison of the medication commercialised in Spain, we found that the authors compared the depot format of fluphenazine with oral antipsychotics chiefly using studies published before 1980 (our review did not consider publications prior to 1980). In addition, when the authors analysed studies comparing depot fluphenazine with another depot drug, they fundamentally compared it with depot haloperidol, which is not sold in Spain. The conclusions with respect to depot fluphenazine are that it does not seem to have any advantages over the oral preparation or over other depot medications in the use of services or symptomatology. Despite this, it seems to cause less adverse effects than the oral antipsychotics.

The review by Dinesh et al[41] (2004): "Depot pipothiazine palmitate and undecylenate for schizophrenia" compared any of these two with another depot antipsychotic or an oral format and with different doses of pipothiazine. The use of studies prior to 1980 should be noted. Regarding the conclusions related to the comparison between depot-oral and depot-depot of the active ingredients available in Spain, the authors concluded that the depot pipotiazine is not statistically different to other depot preparations. Comparisons with oral medication did not inform whether the depot pipotiazine had any advantages or not.

The review of depot risperidone carried out by Hosalli et al[42] (2003) focused on evaluating the evidence of depot risperidone versus oral risperidone or a placebo. In this last group, it should be pointed out that the majority of the studies included were communications made at scientific congresses and published as journal supplements or material provided by the pharmaceutical companies implicated in the marketing of the medications. The authors concluded that there was not enough evidence to support the superiority of depot risperidone over the oral format.

Lastly, the review "Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses" by Coutinho et al[43] (1999), only took into account studies which compared zuclopenthixol with a placebo o with depot haloperidol or depot flupenthixol (which are not sold in Spain).

Discussion

The review confirmed that there was not enough scientific evidence to support that the depot antipsychotics had greater efficacy over the oral antipsychotics. Furthermore, the quality of the selected studies was moderately-low; the main limitation of the articles was that they did not describe the randomisation procedure in detail or the comparison of the depot and oral formats was not double-blind.

However, there are two articles that explain the design type as "non-inferiority trials". Along these lines, a methodological annotation is required: on undertaking a non-inferiority or equivalence trial, the key point of the study is the power, that is, the difference between 1 and the beta or type II error. The beta error is related to not rejecting the void hypothesis when it is in fact false and therefore, if the aim of the study is to find no differences, it should be minimised. The studies which point out that the design is of non-inferiority should make this idea explicit. Taking into account that the alpha and beta error are related, if an alpha of 0.05 is marked, everything seems to signal that this idea has not been made explicit. Similarly, the articles that do not find differences but centre on alpha errors, can only affirm with certainty that the void hypothesis cannot be rejected, which, methodologically does not mean it is accepted. Only one of the studies selected points out this idea.[28] The study by Rabinowitz et al[29] does not express it. In spite of everything, the format of the study, poster communication, may have conditioned this idea.

Depot risperidone

There is little evidence referring to depot risperidone and the existing evidence is contradictory. Two of the studies

TABLE 4 **Evidence table. Pharmaco-economic studies**

Active ingredient	Authors	Context	Aim: is the question of the study well defined?	Method	Costs considered	Results	Sensibility analysis	Limitations
Depot risperidone versus oral olanzapine and depot haloperidol	De Graeve et al[38] (2005)	Specialised care in Belgium schizo-phrenic patients	Evaluate which is the most effective treatment strategy in	Study of the cost-efficiency using a three-branch decision tree (corresponding to the evaluated alternatives). Using TreeAge DATA software. Panel of experts (11 psychiatrists -Delphi method) and literature review. Features of the group based on the evaluation: patients diagnosed with schizophrenia (maximum 5 years) under treatment minimum 1 year. Four health conditions are used: *a)* clinical response (those who relapse and those who do not); *b)* clinical deterioration, defined as positive symptoms, behavioural problems, suicide ideation and extrapyramidal symptoms; *c)* inadequate response;	Costs were assessed using the perspective of the Belgian health system, considering 2003 prices marked by the Institut National D'Assurance Maladie Invalité and the Belgian Ministry of Health. Daily costs are considered according to the place of treatment, visits to community attention, differentiated among widowed patients, orphans, invalids, pensioners and non-pensioners and the pharmaceutical cost according to the dose and frequency. Prices in euros	The most effective strategy is the depot risperidone, with 82.7% of the patients treated effectively, compared with 74.8% with oral olanzapine	Five different credibility analyses were performed, modifying the effectiveness proportion related with the different therapeutic strategies and the proportion of VIPO patients. All of the depot risperidone display better cost-efficiency	Data on efficiency of the therapeutic strategies are based on only three studies. The authors do not inform of the features of the studies used, the sources from which they were chosen, the methods to do so or the quality criteria considered. Indirect costs were not considered. The authors mix the estimated data of effectiveness drawn from the literature with the data estimated by the panel of experts

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TABLE 4 **Evidence table. Pharmaco-economic studies** *(Continuation)*

Active ingredient	Authors	Context	Aim: is the question of the study well defined?	Method	Costs considered	Results	Sensibility analysis	Limitations
				d) hospitalisation. Two year timeframe divided into 6 four-month periods. If at the end of each period, patients experience an inadequate response or clinical deterioration, the drug may be changed. Treatment strategies: depot risperidone: 25mg every fourteen days; depot haloperidol: 100mg every 28 days or 125mg every 28 days; oral olanzapine: 10mg daily				
Depot risperidone versus oral olanzapine and depot haloperidol	Yang et al[39] (2005)	Primary and secondary care in Taiwan	Study whether an increase in the therapeutic fulfilment using depot risperidone, compared with oral olanzapine and depot haloperidol increases the effectiveness and cost-efficiency	Study of cost-efficiency using the model of decision analysis. Estimations are drawn from literature review and expert opinion. Features of the hypothetical group created: cohort of 1,000 patients with schizophrenia under 35, diagnosed in the last 5 years and undergoing treatment for at least 1 year	Economic costs are estimated with data from 200,000 patients and the price of other countries. The authors state that these can be representative of prices in 2001 and are stated in Taiwan dollars	The response rate after 2 years was 0.55 for depot risperidone; 0.32 for depot haloperidol and 0.45 for oral olanzapine. For model 1, the costs were 374,187 dollars for depot risperidone; 315,834 for depot haloperidol and 381,285 for oral olanzapine. For model 2, the costs were 252,885	Sensibility analysis was carried out showing an increase in response of the risperidone by 5, 10 or 15%, but the reason is not provided nor are the methods described	The selection criteria for the literature used to define the features and transitions is not stated. One of the experts was a representative from the pharmaceutical company that commercialises depot risperidone. Indirect costs were not considered

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TABLE 4 **Evidence table. Pharmaco-economic studies** *(Continuation)*

Active ingredient	Authors	Context	Aim: is the question of the study well defined?	Method	Costs considered	Results	Sensibility analysis	Limitations
				The patients receive a score of < 40 on the BPRS scale. States considered are: *a)* response (good response reduction of 20% in symptomatology evaluated with the BPRS); *b)* clinical deterioration, defined as positive symptoms, behavioural problems, suicide ideation and extra-pyramidal symptoms, and *c)* inadequate response. Two models are performed: the first assumes that all the patients receive all the psychiatric interventions (community attention, day hospital, acute unit, home-care services and rehabilitation services over 2 years); the second model assumes that only some patients receive psychiatric intervention when necessary		dollars for depot risperidone; 160,036 for depot haloperidol and 244,055 for oral olanzapine. Cost-efficiency reason: in model 1, 678,367 dollars for depot risperidone; 1,000,741 for depot haloperidol and 841,875 for oral olanzapine. In model 2, 458,457 dollars for depot risperidone; 529,265 for depot haloperidol and 538,872 for oral olanzapine		

concluded that the depot medication proved to be safer than the oral drug in the reduction of adverse effects, but both articles presented data from the same study, although at two different moments in time, at 12 and 48 weeks. The first of these explains that the depot risperidone would be safer in the prevention of laxity, dry mouth and an increase in prolactin concentrations. The second, in poster format, does not explain for which adverse effects the depot risperidone is more effective. On the other hand, the study by Chue et al[28] does not detect any differences between the depot and oral formats. The Rabinowitz study which compares depot risperidone with oral olanzapine did not detect any differences either. The two studies by Bai et al[26,27] point to the superiority of the depot format, although it is also noted that the depot format carries an increase of the positive symptomatology assessed with the PANSS.

The Cochrane review reaches our same conclusions: there are very few thorough studies and the evidence available to date does not allow us to confirm that, in the case of risperidone, one format is better than another.

Only one study compares the depot risperidone with another depot antipsychotic: zuclopenthixol.[34] This study indicates that risperidone is superior to zuclopenthixol when the result measurement is the reduction of substance abuse. In any case, the quality of this study is moderately-low, since it is not double-blind and does not describe the randomisation procedure. Furthermore, participants in the study also received psychological treatment, which could confuse the results.

As far as cost-efficiency, the depot risperidone proved to be superior to the oral risperidone, the depot haloperidol and the oral olanzapine. Nevertheless, it should be pointed out that these appraisals are based on panels of experts and systematic reviews, with important limitations: basically, they do not explain how the literature was reviewed and indirect costs were not taken into account. Moreover, they were performed in health system contexts very different to the Spanish model. Generalisation to our context is not recommended.

Depot fluphenazine

The two studies that compare the depot and oral formats of fluphenazine methodologically present a moderately-high quality. However, they are inconsistent. While the study by Levine et al[30] concludes that the depot format is superior to the oral one when dealing with preventing relapses, the study by Schooler et al[31] concludes that there are no differences. At any rate, the Levine study does not have as an objective the comparison of depot and oral, but the effects of treatment discontinuation. Besides, the final sample was reduced to 27 subjects (10 versus 17), which makes it difficult to draw conclusions. The Cochrane review concluded that the depot format is safer when dealing with the prevention of adverse effects.

The studies that compare intermittent depot fluphenazine with oral pimozide are outdated since pimozide is currently not recommended due to the adverse effects it causes.

Compared with other active ingredients also in depot presentation, such as clopenthixol or pipotiazine, the superiority of fluphenazine in reducing symptomatology or the prevention of adverse effects or relapses has not been proven.

To sum up, there is not enough scientific evidence to confirm that the depot fluphenazine is superior to other antipsychotics, either oral or depot.

Depot pipotiazine

No studies were selected comparing depot pipotiazine with another oral antipsychotic as they were all prior to 1980.

The two articles included in this review comparing depot pipotiazine with depot fluphenazine did not find any significant differences.

Depot zuclopenthixol

The three articles selected evaluating zuclopenthixol have a moderately-high quality. The study by Arango et al[25] that compares oral zuclopenthixol with the depot format is aimed at ascertaining which is more efficient when the main result is reduction of violent behaviour. Despite the depot format presenting a slight superiority over the oral one, the method of recording violent behaviour, through records kept by a family member, can suffer from lack of legitimacy. In any case, patients taking the depot format kept to the medication better than the oral patients. This could involve an advantage and recommendation for patients with schizophrenia and violent behaviour.

The study comparing depot zuclopenthixol with depot fluphenazine found no differences. As has been commented, the comparison between the depot zuclopenthixol and risperidone indicates greater efficacy of the risperidone when the aim is reduction of substance abuse.

As in the previous cases, there is very little evidence of quality that would allow us to affirm that the depot zuclopenthixol is clearly superior to the oral format or other types of depot formats.

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