Psychiatry

Risk of Extrapyramidal Syndromes with Haloperidol, Risperidone, or Olanzapine

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OBJECTIVE: To compare the risk of extrapyramidal syndrome (EPS) between risperidone, olanzapine, and haloperidol, taking into account patients' past antipsychotic drug use and past EPS.

METHODS: Data were obtained from the PHARMO-database, containing filled prescriptions of 450 000 community-dwelling people in the Netherlands from 1986 through 1999. We defined cohorts of first-time users of haloperidol, risperidone, or olanzapine aged 15 to 54 years. In the first 90 days of treatment, we assessed the occurrence of EPS, defined as first use of any antiparkinsonian agent. We estimated relative risks of EPS for risperidone and olanzapine versus haloperidol using a Cox proportional hazards model. Patients were subdivided according to prior use of antipsychotic and antiparkinsonian drugs.

RESULTS: We identified 424 patients starting treatment with haloperidol, 243 with risperidone, and 181 with olanzapine. Prior use of antipsychotic plus antiparkinsonian medication was significantly more frequent among users of risperidone and olanzapine than in those using haloperidol (36.2%, 40.3%, and 4.5%, respectively; $p < 0.001$). Within most subgroups of comparable treatment history, patients using risperidone and olanzapine showed reduced risks of EPS compared with haloperidol, although some of these findings did not reach statistical significance (RR 0.03–0.22). However, this was not observed for patients using risperidone who had experienced EPS in the past (RR 1.30; 95% CI 0.24 to 7.18).

CONCLUSIONS: In general, we observed reduced risks of EPS for risperidone and olanzapine compared with haloperidol within subgroups of patients with a similar treatment history. However, the added value of risperidone in patients who have experienced EPS in the past needs further study.

KEY WORDS: atypical antipsychotics, extrapyramidal syndromes, selective prescribing.

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See also page 1659.

One of the most important adverse effects of conventional antipsychotic drugs (APDs) is the extrapyramidal syndrome (EPS), a group of movement disorders that include parkinsonism, akathisia, dystonia, and tardive dyskinesia. Although these symptoms were initially thought to be a prerequisite for the therapeutic effect of APDs, this view was radically altered with the introduction of clozapine in the 1960s. This drug combines an increased antipsychotic efficacy with a low risk of neurologic adverse effects and, for this reason, was called atypical.[1] Based on these observations, several other atypical antipsychotics have been developed and marketed in recent years. Of these, risperidone and olanzapine are the most widely used. Recent meta-analysis[2] of randomized clinical trials indicated that while atypical APDs may not be more efficacious than conventional drugs, they do show fewer extrapyramidal adverse effects.

A general limitation of randomized trials is that patients and treatment methods may differ largely from those seen in clinical practice, making generalization of results difficult. Trials comparing atypical APDs with conventional

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drugs generally included chronically ill hospitalized schizophrenic patients. In contrast, in clinical practice, users of APDs are much more heterogeneous and include patients who are less severely ill, are treated in an outpatient setting, and receive APDs in doses other than those applied in clinical trials.[3] Thus, results from trials need to be confirmed in the everyday clinical setting using observational studies. However, a traditional concern with observational studies regards their potential bias due to the nonrandomized treatment assignment. In the first few years of marketing, new drugs are apt to be prescribed to patients who do not tolerate or who do not respond adequately to older drugs labeled for the same indication.[4] Thus, atypical APDs are likely to be selectively prescribed to patients with an overt susceptibility for EPS, that is, those who developed EPS during previous treatment with APDs. When comparing the risk of EPS between atypical and classical APDs in observational studies, such imbalance in prognostic factors needs to be accounted for. In previous observational studies regarding antipsychotic-induced EPS, this issue was either not addressed[5] or was circumvented by limiting the study to newly treated patients.[6]

We performed a study to compare the risk of EPS between patients using risperidone or olanzapine and those using haloperidol in clinical practice. To account for possible selective precribing of atypical antipsychotics to patients more susceptible to EPS, patients were stratified according to their prior use of antipsychotic drugs and prior EPS.

Methods

SETTING

Data were obtained from the PHARMO system,[7] a database that includes information from drug-dispensing records for all 450 000 residents of 11 Dutch cities. The computerized drug-dispensing records are obtained from outpatient pharmacy files. Since virtually all patients in the Netherlands designate a single pharmacy to fill prescriptions from general practitioners or medical specialists, the PHARMO system provides a complete record of the prescription history of outpatients. For every dispensed prescription drug, the database contains information on the gender and date of birth of the patient, the dispensed drug, prescriber, dispensing date, amount dispensed, and the prescribed dose regimen. The duration of use of each dispensed drug is estimated by dividing the number of dispensed tablets by the prescribed number of tablets to be used per day. Thus, for each patient in the system, drug exposure can be ascertained on a day-to-day basis.[7] The PHARMO database has previously been used to study various types of drug-induced morbidity,[8,9] including EPS.[10] For this study, we used all available data from January 1, 1986, until June 30, 1999.

PATIENTS

We defined a cohort of patients aged 15–54 years who received oral haloperidol, risperidone, or olanzapine for the first time according to their drug-dispensing records (i.e., new users). We only included patients whose first use of haloperidol, risperidone, or olanzapine was between January 1, 1994, and June 30, 1999. Due to switching of APDs, one patient could be a new user of more than one of the studied antipsychotic drugs. Excluded were patients who were enrolled in the PHARMO database for less than three years prior to their first use of the study drug and patients who filled prescriptions for more than one APD at cohort entry. Follow-up was censored when a patient stopped an APD for more than 60 days, when a patient switched to another APD, or after 90 days of follow-up.

OUTCOME DEFINITION

The outcome of the study was first use of any drug indicated for treatment of drug-induced EPS, which was taken as a measure for the occurrence of EPS. These included the anticholinergic antiparkinsonian drugs benzatropine, biperiden, dexetimide, orphenadrine, procyclidine, and trihexyphenidyl. The risk for developing EPS was considered to be instantaneous, meaning that new use of antiparkinsonian medication was assessed from day 1 after initiation of antipsychotic treatment until the end of follow-up. Patients who started the APD and the antiparkinsonian drug on the same day were excluded because such prescribing practice represents prophylactic use of antiparkinsonian medication.

STATISTICAL ANALYSIS

Crude and adjusted relative risks of EPS for risperidone and olanzapine were calculated using a Cox proportional hazards model, establishing users of haloperidol as the reference group. All multivariate Cox models included age at cohort entry, gender, year of cohort entry, and prescriber (general practitioner, psychiatrist, or other/unknown) as covariates, as well as terms for the use of benzodiazepines, lithium, tricyclic antidepressants, and selective serotonin-reuptake inhibitors during follow-up. Furthermore, to control for possible differences in dosing between antipsychotic drugs, we adjusted for mean prescribed dose during follow-up, expressed in chlorpromazine equivalents. Chlorpromazine equivalents were calculated by multiplying the ratio of the mean prescribed daily dose and the recommended daily dose of the prescribed drug by the recommended dose of chlorpromazine. Recommended doses of antipsychotic drugs were adopted from the World Health Organization (WHO).[11]

We assessed possible differences in susceptibility for EPS between users of haloperidol, risperidone, and olanzapine by comparing their prior use of antipsychotic and antiparkinsonian drugs. We distinguished three strata of increasing complexity of prior antipsychotic drug use: (1) patients with no history of APD use in the three years prior to cohort entry; (2) patients with a history of APD use, but with no use of antiparkinsonian medication in this three-year period; and (3) patients who had used both APD and antiparkinsonian medication in the three years prior to cohort entry. For convenience, we shall refer to these strata as no complexity, intermediate complexity, and severe complexity, respectively. To account for possible differences in susceptibility for EPS between patients using different APDs, we calculated relative risks of EPS within each of these strata of complexity. Among patients with severe complexity, residual imbalance in EPS susceptibility was adjusted for by adding an additional term to the multivariate Cox model representing the number of prescriptions for antiparkinsonian drugs in the three years prior to cohort entry. Furthermore, among patients with a history of APD use (intermediate and severe complexity strata), we also adjusted for whether or not patients were free from APDs on the day before cohort entry. Continuous data were compared using a Student's *t*-test; a χ^2 test was used to compare categorical data.

Results

We identified 424 patients who started for the first time with haloperidol, 243 who started with risperidone, and 181 who started with olanzapine. Table 1 shows characteristics regarding their demographics and medication. Especially for haloperidol and risperidone, the prescribed daily dose was lower than recommended by the WHO[11] and the Dutch Pharmacotherapeutic Guidelines.[12] Patients receiving haloperidol were generally treated by a general practitioner, while patients using risperidone or olanzapine were more often treated by a psychiatrist. Sixty-seven patients were new users of more than one of the antipsychotic

drugs studied and contributed to more than one of the cohorts. Most of these subjects first used haloperidol (59.7%).

Patients using risperidone or olanzapine had a significantly higher frequency of prior use of antipsychotic drugs (i.e., intermediate and severe complexity) than patients using haloperidol (Table 1). However, while the portion of antipsychotic-naive patients (i.e., no complexity) remained more or less constant over time among haloperidol users (1994, 74.0%; 1996, 64.7%; 1999, 82.9%), it increased steadily in patients using risperidone (1994, 0.0%; 1996, 19.2%; 1999, 55.6%) and olanzapine (1996, 0.0%; 1999, 25.0%). For those who had a history of APD use, the median time between cohort entry and the most recent previous APD prescription was 48 days. Based on the estimated duration of use of this most recent prescription, we inferred that, on average, 40.9% of these patients were exposed to an APD on the day before cohort entry. This number was lower for patients starting with haloperidol (28.0%) than for those using risperidone (48.1%; $p = 0.002$) or olanzapine (41.0%; $p = 0.060$).

Among patients with severe complexity, those using risperidone or olanzapine had received significantly more prescriptions of antiparkinsonian drugs in the three years prior to cohort entry than those using haloperidol (on average 12, 11, and five prescriptions for users of risperidone, olanzapine, and haloperidol, respectively; $p < 0.05$). Except for haloperidol, patients with severe complexity tended to receive higher doses of APDs (haloperidol 2.3, 2.0, and 2.2 mg; risperidone 2.0, 2.0, and 3.0 mg; olanzapine 7.5, 8.7, and 9.9 mg for patients with no, intermediate, and severe complexity, respectively). In addition, they tended to be treated more often by a psychiatrist and more often receive concurrent lithium treatment (data not shown).

After cohort entry, antiparkinsonian medication was started in 13.2% of the patients using haloperidol, 11.9% of the patients using risperidone, and 5.0% of those using olanzapine. This yielded an adjusted relative risk of 0.57 (95% CI 0.31 to 1.04) for risperidone and 0.19 (95% CI 0.08 to 0.48) for olanzapine compared with haloperidol (Table 2). We then stratified patients according to their complexity of prior APD use. For patients using risperidone, we observed significantly reduced risks of EPS compared with haloperidol among those with no and those with intermediate complexity of prior APD use. However, risperidone showed a slight but nonsignificant increase in risk among patients with severe complexity. Patients receiving olanzapine had a reduced risk of EPS in all three strata, although in the no-complexity and severe-complexity subgroup, this reduced risk did not reach statistical significance. We observed no difference in the degree of antiparkinsonian medication use between patients treated by psychiatrists and those treated by general practitioners in the study population (adjusted RR 1.30; 95% CI 0.71 to 2.39).

Discussion

Not taking into account any differences in prior medication use between patients, we found that those prescribed risperidone or olanzapine had a lower risk of EPS than pa-

Table 1. Characteristics of Users of Haloperidol, Risperidone, and Olanzapine

	Haloperidol (n = 424)[a]	Risperidone (n = 243)	Olanzapine (n = 181)
Age, mean (y)	37	34[b]	35[b]
Gender (%)			
male	195 (46.0)	114 (46.9)	96 (53.0)
female	229 (54.0)	129 (53.1)	85 (47.0)
Duration of follow-up, mean (d)	32	54[b]	64[b]
Prescribed dose,[c] median (recommended dose; mg/d)[11,12]	2.2 (8.0)	2.0 (6.0)	9.0 (10.0)
Prescriber (%)			
general practitioner	308 (72.6)	38 (15.6)[b]	21 (11.6)[b]
psychiatrist	44 (10.4)	160 (65.8)[b]	130 (71.8)[b]
other or unknown	72 (17.0)	45 (18.5)	30 (16.6)
Concurrent medication use (%)			
benzodiazepines	240 (56.6)	125 (51.4)	95 (52.5)
antidepressants			
TCAs	38 (9.0)	28 (11.5)	30 (16.6)[b]
SSRIs	57 (13.4)	48 (19.8)[b]	34 (18.8)
lithium	8 (1.9)	18 (7.4)[b]	12 (6.6)[b]
Complexity of prior APD use (%)[d]			
none	331 (78.1)	81 (33.3)[b]	47 (26.0)[b]
intermediate	74 (17.5)	74 (30.5)[b]	61 (33.7)[b]
severe	19 (4.5)	88 (36.2)[b]	73 (40.3)[b]

APD = antipsychotic drug; SSRIs = selective serotonin-reuptake inhibitors; TCAs = tricyclic antidepressants.
[a]Reference group.
[b]$p < 0.05$, compared with the reference group (Student's *t*-test for continuous data, χ^2 test for categorical data).
[c]Mean prescribed dose of APD treatment during follow-up.
[d]No complexity = no prior APD use; intermediate complexity = prior APD use without prior antiparkinsonian drug use; severe complexity = prior APD use and prior antiparkinsonian drug use, in the three-year period prior to cohort entry.

tients receiving haloperidol. We also found that users of these atypical APDs more often had a history of APD and antiparkinsonian drug use than patients prescribed haloperidol. This indicates that atypical drugs are selectively prescibed to patients who had EPS in the past and thus are likely to be susceptible for future EPS.[13] We subsequently accounted for this difference in susceptibility by stratifying patients according to their prior use of APDs and antiparkinsonian drugs. With the exception of risperidone users who had a history of using both these classes of drugs, we observed reduced risks of antiparkinsonian drug use for the atypical APDs in each of these strata. These relative risks were similar or somewhat lower than those found in previous randomized controlled trials. Meta-analyses of these trials showed relative risks of antiparkinsonian drug use of 0.47 (95% CI 0.38 to 0.59) for risperidone[3] and 0.17 (95% CI 0.14 to 0.21) for olanzapine[14] compared with conventional APDs.

Among patients with a history of using both APDs and antiparkinsonian medication, we found no difference in antiparkinsonian drug use between users of risperidone and users of haloperidol. A similar result was observed in a randomized, controlled study[15] among patients who had disturbing EPS during prior neuroleptic treatment. The absence of such a reduced risk for risperidone in our study may have several explanations. First, it may be related to dosing. While antipsychotic-induced EPS is caused by blockade of central dopamine D_2 receptors, risperidone also antagonizes 5-HT_2 receptors.[16] This can counterbalance the antidopaminergic effect by disinhibition of the dopamine system. However, this compensatory mechanism is thought to diminish as dosing increases.[17] Indeed, we observed that patients in the severe complexity stratum received higher doses of risperidone than those in the other strata (3.0 vs. 2.0 mg/d). Second, the absence of a reduced risk may also be explained by an underlying pathology. Patients who have experienced EPS in the past are likely to have an inherent susceptibility,[13] which is thought to result from a preexisting nigrostriatal dopamine deficiency, that is, preclinical Parkinson disease.[18,19] Possibly, risperidone's 5-HT_2 antagonism cannot compensate for D_2 blockade in patients with an already impaired dopaminergic function. Contrary to risperidone, olanzapine did show a reduced rate of prescribing of antiparkinsonian medication among severe complexity patients. This may be explained by the different pharmacologic profiles of these agents. In addition to 5-HT_2 antagonism, olanzapine also blocks muscarinic receptors,[20] which is known to reduce EPS liability.[21]

Notwithstanding these biological explanations, we must also consider noncausal explanations. In light of the limited number of patients, the absence of a reduced risk among those with a history of both APD and antiparkinsonian drug use may be due to random error. Furthermore, results may have been affected by misclassification of the study outcome or by uncontrolled confounding.

We used prescriptions of anticholinergic antiparkinsonian medication to identify events of EPS in our study population. Although anticholinergic drugs are unlikely to be prescribed for reasons other than EPS in a nonelderly population using APDs, this marker will not have identified all patients with EPS. First, symptoms of EPS may have gone unnoticed by the treating physician. Second, if correctly diagnosed, EPS may also have been treated by reducing the dosage of the APD or by switching to another APD. Relative risk estimates may have been biased when this underestimation of EPS occurrence differs between different antipsychotics. Difference in assessment, diagnosis, or treatment of EPS may especially result from the observed difference in type of prescriber between atypical APDs and haloperidol. However, we observed similar degrees of antiparkinsionian medication prescribing between psychiatrists and general practitioners. Furthermore, the main results of our study did not change when switching of antipsychotic medication was taken as a marker for EPS (data not shown). These observations argue against such a bias.

Table 2. Complexity of Prior Antipsychotic Drug Use Related to Start of Antiparkinsonian Agents

Complexity of Prior Antipsychotic Drug Use[a]	Haloperidol[b]		Risperidone		Olanzapine	
	Events (%)	RR	Events (%)	RR[c]	Events (%)	RR[c]
All pts.	56 (13.2)	1.0	29 (11.9)	0.57 (0.31–1.04)	9 (5.0)	0.19 (0.08–0.48)
No complexity	42 (12.7)	1.0	4 (4.9)	0.22 (0.06–0.77)	2 (4.3)	0.22 (0.04–1.14)
Intermediate complexity	12 (16.2)	1.0	5 (6.7)	0.20 (0.05–0.72)	1 (1.6)	0.03 (0.00–0.42)
Severe complexity	2 (10.5)	1.0	20 (22.7)	1.30 (0.24–7.18)	6 (8.2)	0.14 (0.02–1.15)[d]

APD = antipsychotic drug; SSRIs = selective serotonin-reuptake inhibitors; TCAs = tricyclic antidepressants.
[a]No complexity = no prior APD use; intermediate complexity = prior APD use without prior antiparkinsonian drug use; severe complexity = prior APD use and prior antiparkinsonian drug use, in the three-year period prior to cohort entry.
[b]Reference group.
[c]Calculated using a Cox proportional hazards model, adjusted for age, gender, year of cohort entry, prescriber, concurrent use of benzodiazepines, lithium, TCAs and SSRIs, mean antipsychotic dose during follow-up, whether or not patients were free from APD use immediately before prescribing of the study drug (intermediate and severe complexity strata only), and number of prescriptions for antiparkinsonian drugs prior to cohort entry (severe complexity stratum only).
[d]Because of the small number of events in this comparison, the adjusted Cox model was reduced to include only terms for age, gender, mean antipsychotic dose during follow-up, whether or not patients were free from APD use immediately before prescribing of the study drug, and number of prescriptions for antiparkinsonian drugs prior to cohort entry.

In our study, the recency of prior use of APDs varied between patients. According to the prescription data, many patients were exposed to APDs on the day before starting with haloperidol, risperidone, or olanzapine. Such an acute switch from one APD to another can cause several problems in assessing the occurrence of EPS. First, some patients may have been exposed to the old and the new APD simultaneously, either because an overlap approach was used in switching individuals from one drug to the other or because the prior APD was not completely eliminated at the time the new drug was started.[22] Second, any extrapyramidal symptoms that existed prior to switching may have persisted while the patient received the new treatment. Taken together, APD use immediately before cohort entry may have increased the risk of EPS. This problem also occurs in many randomized clinical trials, explaining why increased EPS rates often are observed among patients receiving placebo.[23] To control for this potential confounding effect, in our study relative risk estimates were adjusted for whether or not patients were free from APDs in the period immediately before cohort entry.

We had no information on psychiatric diagnosis or disease severity of our study population. However, previous studies[24,25] found that severity of psychopathology is not associated with the risk of EPS. Although disease severity may affect antipsychotic dosing and thus indirectly influence EPS rates, dosing was adjusted for in the analysis. Thus, any differences in severity of psychopathology between patients using different APDs are unlikely to have biased the results of our study.

Summary

Based on the results of our study, we can conclude that, since atypical antipsychotics are selectively prescribed to patients with a history of EPS, a patient's disease history should be taken into account when comparing the risk of future EPS between atypical and conventional APDs. Stratifying on prior use of APDs and antiparkinsonian drugs, we found that patients using olanzapine have a strongly reduced risk for EPS compared with those using haloperidol. This was also observed for risperidone, except in the subgroup of patients who had experienced EPS in the past. The added value of risperidone in this patient group needs further study.

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EXTRACTO

OBJETIVO: Comparar la risperidona, el haloperidol y la olanzapina en cuanto al riesgo de desarollar el síndrome extrapiramidal (EPS), tomando en cuenta la historia del uso de drogas antipsicóticas e historia pasada de EPS.

MÉTODOS: Se obtuvieron datos a partir del PHARMO-database, una base de datos conteniendo información de las recetas médicas de 450 000 residentes de los Países Bajos durante el período de 1986–1999. Se identificaron cohortes de pacientes entre 15 y 54 años de edad quienes estaban usando haloperidol, risperidona, o olanzapina por primera vez. Durante los primeros 90 días de tratamiento se evaluó la ocurrencia de EPS, definido como el primer uso de cualquier agente antiparkinsoniano. Se estimaron los riesgos relativos de EPS para risperidona y olanzapina comparados con haloperidol usando el modelo Cox de riesgos proporcionales. Se dividieron los pacientes en base a su uso anterior de drogas antipsicóticas y antiparkinsonianas.

RESULTADOS: Se identificaron 424 pacientes comenzando tratamiento con haloperidol, 243 con risperidona, y 181 con olanzapina. Uso anterior de agentes antipsicóticos y antiparkinsonianos fue reportado mas frecuentemente en los sujetos tomando risperidona y olanzapina que en el grupo usando haloperidol (36.2%, 40.3%, y 4.5%, respectivamente; $p < 0.001$). En la mayoría de los sub-grupos con una historia de tratamiento comparable, los sujetos usando risperidona y olanzapina demostraron menos riesgo de EPS comparado con los tomando haloperidol, aunque algunos no alcanzaron importancia estadística (RR entre 0.03 y 0.22). Sin embargo, sujetos en el grupo de risperidona con una previa historia de EPS demostraron mas riesgo (RR 1.30; 95% CI 0.24–7.18).

CONCLUSIONES: En general, observamos menos riesgo de EPS para risperidona y olanzapina comparados con haloperidol entre los sub-grupos con comparable historia médica. Sin embargo, el papel de risperidona en pacientes que han sufrido anteriormente de EPS merece mas estudio.

Christina Dalmady-Israel

RÉSUMÉ

OBJECTIF: Comparer les risques d'apparition de syndromes extrapyramidaux (SEP) attribuables au traitement par la rispéridone, l'olanzapine et l'halopéridol, en tenant compte des autres médicaments antipsychotiques utilisés antérieurement et de présence ou non de SEP antérieurs chez le patient.

MÉTHODOLOGIE: Les données ont été obtenues à partir d'une recherche dans la banque informatisée Pharmo contenant des informations sur les ordonnances remplies chez 450 000 personnes vivant dans la communauté aux Pays-Bas entre 1986 et 1999. Des cohortes de nouveaux utilisateurs d'halopéridol, de rispéridone ou d'olanzapine âgés de 15 à 54 ans ont été identifiées. Durant les premiers 90 jours de traitement, l'occurrence de cas de SEP a été évaluée en se basant sur la première fois qu'un agent antiparkinsonien a été utilisé chez un patient. Le risque relatif de SEP pour la rispéridone et l'olanzapine par rapport à celui de l'halopéridol a été déterminé selon le modèle de Cox. Les patients ont été regroupés selon l'emploi antérieur d'agents antipsychotiques et antiparkinsoniens.

RÉSULTATS: Ont été identifiés 424 patients chez lesquels un traitement par l'halopéridol a été instauré, 243 par la rispéridone et 181 par l'olanzapine. L'emploi antérieur d'agents antipsychotiques et antiparkinsoniens était significativement plus fréquent chez les utilisateurs de rispéridone et d'olanzapine que chez ceux qui recevaient l'halopéridol (36.2%, 40.3%, et 4.5%, respectivement; $p < 0.001$). Dans les sous-groupes de patients ayant un passé médicamenteux comparable, les utilisateurs de rispéridone et d'olanzapine ont montré une réduction du risque de SEP comparativement aux utilisateurs d'halopéridol, non statistiquement significative dans tous les cas (RR entre 0.03 et 0.22) contrairement aux observations chez les utilisateurs de rispéridone ayant une histoire de SEP (RR 1.30; 95% IC 0.24–7.18).

CONCLUSIONS: En général, on observe une forte réduction du risque de syndromes extrapyramidaux pour la rispéridone et l'olanzapine comparativement à l'halopéridol dans les sous-groupes de patients ayant une histoire de la maladie comparable. Cependant, la valeur ajoutée de la rispéridone chez les patients qui ont présenté des SEP antérieurs n'est pas montrée, une étude plus poussée est nécessaire.

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