

ORIGINAL ARTICLE

Neurological syndromes associated with drug use. Frequency and characterisation^{☆,☆☆}

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KEYWORDS

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Adverse drug reaction;
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Drug;
Neurological syndromes;
Unavoidable adverse event

Abstract

Introduction: The need for safe health care, in which the care and treatment of the patient does not cause any injuries in addition to those already arising from their baseline disease, has led to the present study. Our objective has been to determine the frequency and describe the neurological syndromes attributable to drugs, their preventability and the levels of medical care involved.

Methods: Observational study. Cohort of subjects referred from Primary and Specialised Care between December 2008 and January 2010 due to neurological symptoms attributable to drugs, and previously known neurology patients who began to have symptoms other than those of the baseline disease, also caused by drugs. The notifications were recorded in a questionnaire. Frequency distributions, central tendency measurements, χ^2 or Fisher tests and non-parametric tests were performed.

Results: The prevalence of adverse neurological events was 0.586% of the total sample. Of the 105 patients selected, the most frequent adverse events were: 25.7%, akinetic-rigid syndrome, 18.1%, dyskinetic syndrome, 11.4% neuro-psychiatric symptoms, and 10.5% confusional syndrome. The most commonly recorded pharmacological groups were, in decreasing order: anti-epileptic, dopaminergic, antidepressant, neuroleptic, antiveriginous and prokinetic drugs. We describe the most susceptible population and the statistically significant relationships between the presence of certain pharmacological groups and neurological syndromes.

Conclusions: The low prevalence detected may be due to the study design, although adverse neurological events accounted for 2.84% of the admissions to a Neurology Unit. Understanding the epidemiology should help us to identify the safest approaches, apply them correctly to the population at a higher risk, and reduce healthcare needs and consumption of medical resources.

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PALABRAS CLAVE

Efecto adverso;
Efecto adverso
evitable;
Efecto adverso
inevitable;
Fármaco;
Reacción adversa
medicamentosa;
Síndrome neurológico

Síndromes neurológicos asociados al uso de medicamentos. Frecuencia y caracterización**Resumen**

Introducción: La necesidad de una asistencia sanitaria segura en la que los cuidados y tratamientos no supongan daños diferentes a los derivados de la enfermedad de base, ha motivado este estudio. Nuestro objetivo ha sido determinar la frecuencia y describir los síndromes neurológicos atribuibles a fármacos, su evitabilidad y los niveles asistenciales implicados.

Métodos: Estudio observacional. Cohorte prospectiva de todos los sujetos derivados desde atención primaria y especializada, en el período de diciembre de 2008 a enero de 2010, por síntomas neurológicos atribuibles a fármacos y enfermos neurológicos conocidos con clínica distinta o agravada de la enfermedad de base causada por fármacos. Las notificaciones quedaron reflejadas en un cuestionario. Se realizaron distribuciones de frecuencias, medidas de tendencia central, pruebas de la χ^2 o Fisher y pruebas no paramétricas correspondientes.

Resultados: La prevalencia de efectos adversos neurológicos respecto a la muestra total fue 0,586%. De los 105 pacientes seleccionados, los principales efectos adversos fueron: 25,7% síndrome rígido-acinético; 18,1% discinético; 11,4% síntomas neuropsiquiátricos, y 10,5% síndrome confusional. Los grupos farmacológicos más registrados fueron, en orden decreciente: antiepilépticos, dopaminérgicos, antidepresivos, neurolépticos, antivertiginosos y procinéticos. Describimos la población más susceptible y las asociaciones estadísticamente significativas entre la presencia de determinados grupos farmacológicos y síndromes neurológicos concretos.

Conclusiones: La baja prevalencia detectada puede deberse al diseño del estudio, aunque los efectos adversos neurológicos suponen el 2,84% de los ingresos en una unidad de neurología. Conocer la epidemiología permitirá identificar los abordajes más seguros, aplicarlos correctamente a la población de mayor riesgo y reducir necesidades asistenciales y recursos médicos.

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Introduction

There is an increasing interest in the risks and adverse events within the health field, as patient safety has emerged as a fundamental goal in healthcare. With this in mind, the World Health Organization launched the "World Alliance for Patient Safety" and defined the quality of care as follows: proper diagnosis and treatment for the patient (scientific and technical quality), according to current medical knowledge and biological factors (achievable optimal state of health), with a minimum cost in resources (efficiency), minimum exposure to the risk of additional harm (risk management), and maximum patient satisfaction.^{1,2}

Higher life expectancies produce additional healthcare needs; a higher degree of socioeconomic development requires better quality of care and more information; and the increasing complexity of the diagnostic technologies and treatment resources causes sustainability problems within healthcare systems. Therefore, one of the priorities in healthcare is to identify the safest and most effective diagnostic procedures and treatments, and to ensure that such procedures and treatments do not cause harm or complications other than those from the underlying disease. At the very least, doctors must assess the risks and benefits of medical interventions in cases in which additional harm is expected and cannot be prevented.³⁻⁵ Although measuring the level of risk for a patient in contact with healthcare services is a difficult task, we must be well aware of the frequency and severity of medical incidents, accidents and errors, as has been recommended in recent years.⁶⁻¹⁰

Studies have been carried out at the international level to address patient safety within the healthcare environment. The study of reference was performed in 1984 in New York (Harvard Medical Practice Study, HMPS).¹¹ This study estimated an ADE (adverse drug event) incidence rate of 3.7% in the 30 121 medical records that were revised. Subsequent studies have shown AE (adverse event) rates ranging between 2.9%¹² and 7% to 16%.¹³⁻¹⁶ The study by Healey et al.¹⁷ revealed the highest AE rates: in a sample of 4743 patients monitored prospectively, 31.5% of the patients experienced AEs. In 2002, a French pilot study coordinated by the *Comité de Coordination de l'Évaluation Clinique et de la Qualité en Aquitaine* was completed in order to establish the basis for France's national study (ENEIS).¹⁸ In 2004, Proyecto IDEAS was published in the Region of Valencia (Spain) and subsequently used as a pilot project for ENEAS, Spain's national study, in 2005.¹⁹ In this study, researchers found that the incidence of patients with AEs directly related to hospital care was 8.4%.²⁰ Completed in 2008, the APEAS study is the most recent national-level study carried out in Spain, and it specifically addresses patient safety at the primary care level. Of the total recorded AEs, 47.8% of the cases were drug-related, and 5.1% were drug-induced neurological alterations.²¹

We did not find any Spanish studies that addressed the specific problem of AEs presenting with neurological symptoms. The main purpose of this study is to determine the frequency and types of drug-induced neurological syndromes. Its secondary objectives are to determine the association between AE and comorbidities, polytherapy, sex,

age, and pharmacological group; and to assess preventable AEs, the time elapsed before the syndrome resolves, and the levels of care from which the drugs were prescribed.

Subjects and methods

We designed an observational study of a prospective cohort of patients included between December 2008 and January 2010. Patients were monitored until June 2010.

We analysed all subjects older than 14 years referred to the neurology department by primary care doctors or specialists by way of the emergency department, other hospital departments, or outpatient clinics. During the inclusion period, a total of 17 896 patients were assessed. There were 3936 initial consultations, 13 167 follow-up visits, and 793 hospital admissions. From the total, we selected those patients seeking a neurological consult for a reason shown by the initial assessment to be potentially drug-related. We also selected patients with known neurological conditions who made appointments due to unrelated symptoms or exacerbation of the underlying disease that could be drug-related ($n=133$). All patients in the initial selection were monitored for 6 months. Inclusion was definitive for patients whose clinical check-ups and subsequent complementary tests ruled out other aetiologies to confirm a pharmacological cause. This aetiology was supported by the complete resolution of all neurological symptoms the patients suffered; statistical studies were carried out for those symptoms ($n=105$). We excluded those patients whose neurological symptoms were due to neurological disease and not caused by medication (as determined at the time of the initial evaluation or after receiving the complementary test results). We also excluded patients who left the study and those whose results were not available at the end of the study period because definitive complementary tests were pending. We excluded patients whose medications suspected of provoking ADEs could not be suspended due to ethical reasons (e.g. patients with heart disease requiring antiarrhythmic agents) or treatment dependence (e.g. psychiatric patients requiring additional time to confirm pharmacological origin of symptoms following a change in neuroleptics or anxiolytic drugs), and any patients still presenting neurological symptoms at the end of the follow-up period. This may have resulted in the exclusion of cases in which syndromes required a longer washout period or were not reversible, such as tardive dyskinesias.

We did not study the adverse effects of procedures such as lumbar puncture.

We obtained the approval of the ethics committee and the research unit pertaining to the centre where the study was conducted.

The study was performed in a hospital whose neurology department included 16 beds, 4 hospital outpatient clinics and on-call neurologists. This centre, a secondary hospital in Castile-La Mancha (Ciudad Real, Spain), provides care to an area with 223 669 inhabitants. In order to calculate the sample size, we used the information collected by the APEAS study²¹ regarding patient safety in primary care.

Three professional categories participated in the initial selection of subjects: neurology specialists, neurologists, and a neurology resident who had received specific training

in clinical pharmacology for neurologists. Participating professionals received the appropriate instructions so as to prevent biases.

During the initial evaluation, the participants initially selected a total of 133 candidates for the study. They recorded data identifying the patients, the suspicious drug, and the neurological syndrome by filling in a specific form that was modified from the APEAS study questionnaire (Fig. 1).²¹ This form was drawn up according to consensus and based on a preliminary study with a list of conditions similar to that used in the New York,¹³ Utah, and Colorado studies.¹⁴ The drug was discontinued and patients were given appointments for check-ups at a later date. They were reassessed at that time and complementary laboratory and imaging tests were ordered where necessary. Changes during the follow-up period are shown in the patients' medical histories. Data were delivered to two reviewers (a specialist and a supervised resident) who analysed all the medical histories before definitively selecting the 105 patients. Using this questionnaire, we created the database for statistical analysis.

We employed the universal taxonomy developed by organisations such as the World Health Organization or the Joint Commission on Accreditation of Health Care Organizations (JCAHO).²²

We studied the following variables: neurological syndrome (as an adverse effect), preventability, and time for the symptoms to resolve. Independent variables in the analysis were as follows: pharmacological group, level of care, comorbidities, age, sex, and polytherapy. Table 1 shows the operational definitions for the study.

Data were processed using PASW Statistics 18. In the data analysis, we used descriptive statistics for qualitative and quantitative variables. We calculated statistical associations among the qualitative variables by using the chi-square test or the Fisher exact test. Differences among groups for the quantitative and continuous variable 'age' were assessed using the Mann–Whitney *U* test; rank differences for ordinal variables were measured with the Kruskal–Wallis test.

Patient confidentiality was maintained.

Results

Thirteen neurology professionals contributed to the study and 17 896 patients were treated during the study period. Based on the initial evaluation, we identified 133 cases of possible neurological syndromes caused by ADE; 105 patients were included in the definitive study. Of the 28 patients who were excluded, 4 had a very high probability of ADE with effects persisting at the end of the study (tardive dyskinesias) and 6 were excluded due to the difficulty of exchanging the harmful drug for another in view of comorbidities and the difficulties of interdisciplinary management (e.g. amiodarone in patients with cardiac arrhythmia). Another 11 had an underlying disease, which was discovered in some cases because of medication (Parkinson's disease and dopamine depletion secondary to neuroleptics). We were unable to confirm diagnosis in 7 patients since they were lost to follow-up or because the study period ended. Of the total of included patients, 5 experienced 2 or more AEs. One patient with myasthenia gravis became critical

as a result of 3 myasthenic crises; another patient presented 2 demyelinating episodes with no known neurological history; the remaining 3 patients, all diagnosed with Parkinson's disease, each experienced exacerbations on 2 different occasions.

Of the patient total, 21% of the cases were admitted to hospital (consults requested by other departments are included in this percentage), 19% were referred by

the emergency department, and 59% were referred by neurology outpatient clinics.

Males included in the study accounted for 29.5% of the total number of patients (95% CI, 20.7%–38.2%), with women comprising the remaining 70.5% (95% CI, 61.7%–79.2%). The mean age was 62.12 years. Men had a mean age of 57.32 years (95% CI, 47.89–66.75; SD = 25.7) and women had a mean age of 64.14 years (95% CI, 59.42–68.85; SD = 20.34).



Formulario para la identificación de Incidentes y EA en Atención Primaria

Datos del centro	Datos del paciente:
Tipo de centro <input type="checkbox"/> Urbano <input type="checkbox"/> Rural	Caso : _____
Categoría profesional <input type="checkbox"/> Médico de familia <input type="checkbox"/> Pediatra <input type="checkbox"/> Enfermera <input type="checkbox"/> MIR	Edad : _____ <input type="checkbox"/> Hombre <input type="checkbox"/> Mujer
Experiencia laboral <input type="checkbox"/> Menos de 1 año <input type="checkbox"/> De 1 a 5 años <input type="checkbox"/> De 5 a 10 años <input type="checkbox"/> más de 10 años	Fecha de la notificación: ____/____/____ Fecha del suceso: ____/____/____ <div style="display: flex; justify-content: space-around;"> dd mm aa aa </div>

1.- Indicar si el paciente presenta alguno de los siguientes factores de riesgo.

F.R. INTRÍNSECO

- | | | |
|--|---|--|
| <input type="checkbox"/> Insuficiencia renal | <input type="checkbox"/> Drogadicción | <input type="checkbox"/> Hipertensión |
| <input type="checkbox"/> Diabetes | <input type="checkbox"/> Obesidad | <input type="checkbox"/> Alcoholismo |
| <input type="checkbox"/> Neoplasia | <input type="checkbox"/> Hipoalbuminemia | <input type="checkbox"/> Hipercolesterolemia |
| <input type="checkbox"/> Inmunodeficiencia | <input type="checkbox"/> Úlcera por presión | <input type="checkbox"/> Depresión |
| <input type="checkbox"/> Enfermedad pulmonar crónica | <input type="checkbox"/> Malformaciones | <input type="checkbox"/> VIH |
| <input type="checkbox"/> Neutropenia | <input type="checkbox"/> Insuficiencia cardíaca | <input type="checkbox"/> Malaria |
| <input type="checkbox"/> Cirrosis hepática | <input type="checkbox"/> Enfermedad coronaria | |

F.R. EXTRÍNSECO

- | | | |
|---|--|---|
| <input type="checkbox"/> Sonda urinaria abierta | <input type="checkbox"/> Traqueostomía | <input type="checkbox"/> Colostomía |
| <input type="checkbox"/> Sonda urinaria cerrada | <input type="checkbox"/> Terapia inmunosupresora | <input type="checkbox"/> Sonda nasogástrica |
| <input type="checkbox"/> Nutrición enteral | | |

2.- Resuma que es lo que ocurrió y cuál cree usted que fue la causa:

3.- ¿En qué nivel asistencial ocurrió el problema?

- | | |
|---|--|
| <input type="checkbox"/> Atención urgente en atención primaria | <input type="checkbox"/> Ingreso hospitalario previo |
| <input type="checkbox"/> Consultas médicas de atención primaria | <input type="checkbox"/> Consultas de atención especializada |
| <input type="checkbox"/> Consultas de enfermería de atención primaria | <input type="checkbox"/> Farmacia |
| <input type="checkbox"/> Urgencias del hospital | <input type="checkbox"/> Otros (herboristería, fisioterapia,...) |

Figure 1 Data collection form used in the APEAS study.

5.- Señale todos los efectos que se produjeron en el paciente:**Relacionados con un procedimiento**

- ☐ Hemorragia o hematoma relacionadas con intervención quirúrgica o procedimiento
- ☐ Hematuria relacionada con sondaje
- ☐ Trastorno circulatorio (férula muy ajustada)
- ☐ Dehiscencia de suturas
- ☐ Serosas, abscesos o granulomas
- ☐ Perforación timpánica
- ☐ Otras complicaciones debidas a un procedimiento

Relacionados con infección nosocomial

- ☐ Infección de herida quirúrgica v/o traumática
- ☐ ITU asociada a sondaje
- ☐ Bacteriemia asociada a dispositivo
- ☐ Infección oportunista por tratamiento inmunosupresor o uso de antibióticos
- ☐ Infección de úlcera por presión
- ☐ Neumonía por aspiración

Relacionados con los cuidados

- ☐ Flebitis
- ☐ Úlcera por presión
- ☐ Quemaduras, erosiones, caídas y contusiones (incluyendo fracturas consecuentes)
- ☐ Lesión de ciático por inyectables
- ☐ Otras consecuencias de los cuidados

Generales

- ☐ Peor curso evolutivo de la enfermedad de base
- ☐ Necesidad de repetir el procedimiento o vista
- ☐ Ansiedad, estrés o depresión

Relacionados con la medicación

- ☐ Náuseas, vómitos o diarrea secundarios a medicación
- ☐ Malestar o dolor por fármacos (epigastralgia)
- ☐ Prurito, rash o lesiones dérmicas reactivas a fármacos o apósitos
- ☐ Manifestaciones alérgicas sistémicas
- ☐ Cefalea por fármacos
- ☐ Alteraciones neurológicas por fármacos
- ☐ Estreñimiento
- ☐ Otros efectos secundarios (tos, disnea, sequedad de boca,...)
- ☐ Hipotensión por fármacos
- ☐ Mal control de la tensión arterial
- ☐ Hemorragia digestiva alta
- ☐ Hemorragia por anticoagulación
- ☐ IAM, AVC, TEP, TVP
- ☐ Desequilibrio de electrolitos
- ☐ Edemas, insuficiencia cardíaca y shock
- ☐ Alteración del ritmo cardíaco o actividad eléctrica por fármacos
- ☐ Alteración funcional (renal, hepática, triodea,...)
- ☐ Mal control de la glucemia
- ☐ Neutropenia
- ☐ Efectos locales o fiebre tras vacuna o fármaco mal manejo del dolor

Otras

- ☐ Otra consecuencia
- ☐ Ningún efecto

6.- ¿Qué atención recibió el paciente a consecuencia del efecto adverso?

- ☐ La atención sanitaria no se vio afectada
- ☐ Requirió un nivel más elevado de observación y monitorización en AP.
- ☐ Requirió una prueba adicional (radiografía, análisis,...) en AP.
- ☐ Tratamiento médico o quirúrgico adicional (antibióticos, cirugía menor,...) en AP.
- ☐ Requirió una nueva consulta o derivación a atención especializada o urgencias sin ingreso.
- ☐ Requiere hospitalización: tto de soporte vital (intubación orotraqueal, RCP, intervención quirúrgica).

7.- Indique todos los factores causa les del efecto adverso**relacionados con la medicación**

- ☐ RAM
 - Errores de medicación
 - ☐ Medicamento erróneo
 - ☐ Dosis incorrecta
 - ☐ Omisión de dosis, medicación o vacuna
 - ☐ Frecuencia de administración incorrecta
 - ☐ Error de preparación o manipulación
 - Monitorización insuficiente
 - Error de dispensación
 - Paciente equivocado
 - Duración del tratamiento incorrecta
 - Falta de adherencia al tratamiento
 - Interacción medicamentosa

Relacionados con la gestión

- ☐ Duplicidad de historia clínica
- ☐ Pérdida de documentos
- ☐ Equivocación en la información sanitaria
- ☐ (Resultados de pruebas de otras pacientes)
- ☐ Error en la identificación del paciente
- ☐ Lista de espera prolongada
- ☐ Problemas con la historia informatizada
- ☐ Citación errónea

Relacionados con el diagnóstico

- ☐ Error diagnóstico
- ☐ Retraso en derivación a atención especializada
- ☐ Retraso en el diagnóstico

Figure 1 (Continued).

Table 1 Operational definitions.

Adverse event	Any unexpected accident detected during the consultation which has caused neurological symptoms, whether or not the patient sustained harm (known as 'adverse effect' and incident, respectively), and which results from medical attention (medical error or otherwise) and not from the patient's underlying disease. To determine that healthcare was the cause of the adverse effect, reviewers expressed their degree of confidence that the adverse effect could be due to healthcare as scores on a 3-point scale (where 1 = total lack of evidence and 3 = very solid evidence). Any undesired effect will be referred to as an adverse event so as to simplify terms.
Preventable adverse effect	To determine if the adverse effect was avoidable, reviewers used a score of 0 to indicate lacking or improbable evidence of preventability and a score of 1 to indicate very solid evidence of preventability.
Impact on the patient	Potential effects on health as a result of medical treatment. To evaluate degree of impact, the reviewers used a 5-point scale (where 1 = no effects occurred and 5 = effects occurred and the patient died) to indicate their degree of confidence that the treatment had or may have had an impact on the patient's health.
Level of care	A '0' indicates an adverse effect that occurred in primary care and a '1' indicates an adverse effect in specialised care.
Medical error	Mistake or omission made by health professionals, which may contribute to the appearance of an adverse effect.
Medication error	Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional or patient.
Adverse drug reaction	Effect on and/or harm to the patient when drugs are used properly. They are therefore difficult to avoid.
Comorbidity	Presence of one or more disorders (or diseases) apart from the primary disease or the disorder.
Dyskinetic syndromes	Trembling, chorea, dystonia, tics, myoclonus, ballism, akathisia, restless legs syndrome, etc.
Sensory syndromes	Loss of sensation, hypaesthesia, hyperaesthesia, allodynia, hyperalgesia, paraesthesia, photophobia, dyschromatopsia, visual acuity disorders.
Neuropsychiatric symptoms	Delusions, visions, depression, anxiety, etc.

Table 2 Percentages of observed neurological syndromes.

Neurological syndromes	Frequency	Valid percentage (95% CI)
Akinetic-rigid syndrome	27	25.7 (16–35.3)
Dyskinetic syndrome	19	18.1 (10.7–25.4)
Cerebellar syndrome	5	4.8 (0.7–8)
Sensory syndrome	2	1.9 (0.7–4.5)
Epileptic seizure	8	7.6 (2–12.6)
Headache	2	1.9 (0.7–4.5)
Confusional syndrome	11	10.5 (4.6–16.3)
Coma and disorders of consciousness	2	1.9 (0.7–4.5)
Demyelination syndrome	5	4.8 (0.7–8)
Myasthenic syndrome	4	3.8 (0.2–7.4)
Myopathic syndrome	3	2.9 (0.3–6.1)
Reversible posterior leucoencephalopathy	1	1.0
Neuropsychiatric symptoms	12	11.4 (5.3–17.4)
Cognitive decline	4	3.8 (0.2–7.4)
Total	105	100.0

Tables 2 and 3 show the observed frequencies for neurological syndromes and the causative agents, respectively. Table 4 shows all the neurological syndromes observed in association with different pharmacological groups.

We found most of the akinetic-rigid syndromes in patients undergoing prolonged treatment (some of which lasted years) with antivertigo, prokinetic and antiemetic drugs. Other patients suffered these syndromes due to an

Table 3 Observed frequencies of suspected causative agents.

Suspected pharmacological group	Frequency	Valid percentage (95% CI)
Antiepileptic drugs	17	16.2 (9.1–23.2)
Antiparkinsonian drugs	14	13.3 (6.9–19.7)
Drugs for dementia (cholinesterase inhibitors)	3	2.9 (0.3–6.1)
Neuroleptics/antipsychotics	11	10.5 (4.6–16.3)
Beta blockers	3	2.9 (0.3–6.1)
Antivertigo drugs (including neuroleptics used as antivertigo drugs)	10	9.5 (3.8–15.1)
Prokinetic–antiemetic drugs	9	8.6 (3.2–13.9)
Drugs used in multiple sclerosis (glatiramer acetate, interferon)	1	1.0
Vaccines (flu, human papillomavirus)	5	4.8 (0.7–8.8)
Antidepressants	13	12.4 (6–18.7)
Calcium channel blockers	2	1.9 (0.7–4.5)
Salts (lithium, magnesium) and iodinated contrasts	4	3.8 (0.2–7.4)
Others (NSAIDs, antibiotics, anti-diabetic drugs, statins, diuretics, muscle relaxants, opiate analgesics, antineoplastic drugs, antihistamines)	13	12.4 (6–18.7)
Total	105	100.0

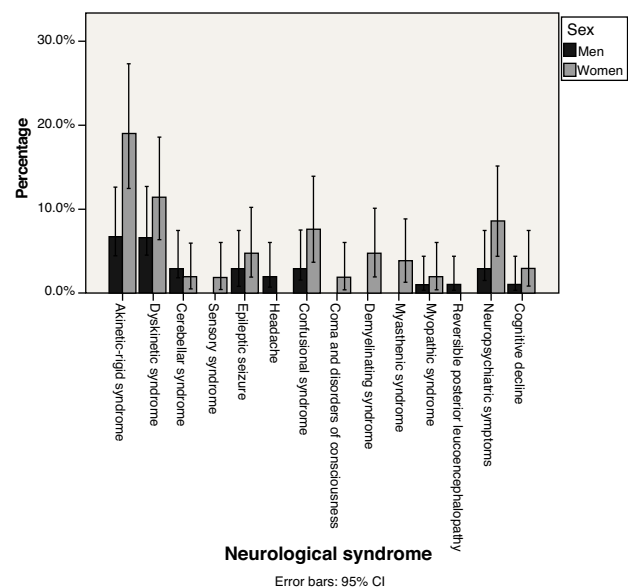
idiosyncratic reaction. Most of the neuropsychiatric symptoms occurred in subjects with long-term neurodegenerative disease receiving treatment with dopaminergic drugs. Among patients showing dyskinetic syndrome, trembling was more common in young subjects receiving antiepileptic treatment (valproic acid).

An interesting result is that there were 4 cases with demyelinating symptoms (5 demyelinating episodes) and a recent history of vaccination (human papillomavirus vaccine in 4 cases and 1 case of influenza vaccine). Only the influenza vaccine case had a history of multiple sclerosis. Concerning the others, 2 met the criteria for multiple sclerosis at a later date and the last subject is currently disease-free.²³ These findings were deduced from our observations, since the statistical analysis did not show this association.

We found significant associations between antiepileptic drugs and dyskinetic syndrome ($P = .013$); dopaminergic drugs and neuropsychiatric symptoms ($P = .000$); antipsychotics/neuroleptics and akinetic-rigid syndrome ($P = .031$); and antivertigo–prokinetic–antiemetic drugs and akinetic-rigid syndrome ($P = .000$).

Fig. 2 shows percentages, broken down by sex, of each of the different syndromes observed. Although we observed that more women than men suffered from each of the different neurological syndromes, statistical analysis did not show that AEs were more common in women than in men ($P = .848$). Table 5 shows the mean ages for each neurological syndrome. We did not find any statistical differences among the main neurological symptoms.

Of the patient total, 75.2% of the cases (95% CI, 66.9%–83.4%) were treated in polytherapy vs 24.8% (95% CI, 16.5%–33%) treated in monotherapy. We did not find any statistical associations between polytherapy and the presence of certain neurological syndromes. Of the patients with identified AEs, 89.5% presented comorbidities while 10.5% did not (Fig. 3). The most frequent comorbidity, accounting for 45.7% of the cases, was prior neurological disease. Comorbidities were as follows, in descending order

**Figure 2** Percentages of the different neurological syndromes observed, broken down by sex.

of frequency: Parkinson's disease, epilepsy, headache, essential tremor, cognitive decline, cerebrovascular disease, demyelinating disease, myasthenia gravis, and brain tumour. Non-neurological comorbidities were as follows: history of psychiatric disorder in 28.6% and 2 or more cardiovascular risk factors in 11.4%.

After recategorising symptoms into specific neurological syndromes, we found more AEs in patients with prior neurological disease ($P = .042$; 95% CI, 36.1%–55.2%), mainly neuropsychiatric symptoms, followed by akinetic-rigid syndrome, dyskinetic syndrome, and confusional syndrome (Fig. 4). On the other hand, we did not find any association with a history of psychiatric disorder ($P = .742$).

Table 4 Counts for different neurological syndromes and pharmacological groups in sample.

Count	Neurological syndrome													
	Akinetic-rigid synd.	Dyskinetic synd.	Cerebellar synd.	Sensory synd.	Epileptic seizure	Headache	Confusional synd.	Coma	Demyelination	Myasthenic synd.	Myopathic synd.	RPLS	Neuropsychiatric symptoms	Cognitive decline
Antiepileptics	2	7	2	0	2	0	1	2	0	0	0	0	0	1
Antiparkinsonian drugs	2	1	0	0	0	0	3	0	0	0	0	0	8	0
Dementia drugs	0	0	0	0	1	0	0	0	0	0	1	0	1	0
Neuroleptics/antipsychotics	6	2	0	0	2	0	0	0	0	0	0	0	0	1
Beta blockers	0	0	0	0	0	2	0	0	0	0	0	0	1	0
Antivertigo drugs	8	1	0	0	0	0	1	0	0	0	0	0	0	0
Prokinetic—antiemetic drugs	5	4	0	0	0	0	0	0	0	0	0	0	0	0
Multiple sclerosis drugs	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Vaccines (flu, HPV)	0	0	0	0	0	0	0	0	5	0	0	0	0	0
Antidepressants	4	3	1	1	0	0	3	0	0	0	0	0	1	0
Calcium channel blockers	0	0	0	0	0	0	0	0	0	1	0	0	1	0
Salts (lithium, magnesium) and iodinated contrasts	0	0	1	0	0	0	0	0	0	3	0	0	0	0
Antidiabetic drugs	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Other drugs (NSAIDs, antibiotics, statins, diuretics, muscle relaxants, opiate analgesics, antineoplastic drugs, antihistamines)	0	1	1	1	3	0	2	0	0	0	1	1	0	2

RPLS: reversible posterior leucoencephalopathy; HPV: human papillomavirus vaccine.

Table 5 Neurological syndromes and ages in sample.

Neurological syndrome		Statistic		
Age (years)	Akinetic-rigid syndrome	Mean		66.96
		95% confidence interval	Lower limit	58.33
			Upper limit	75.60
	Dyskinetic syndrome	Standard deviation		21.834
		Mean		63.00
		95% confidence interval	Lower limit	50.87
	Cerebellar syndrome		Upper limit	75.13
		Standard deviation		25.164
		Mean		56.60
	Sensory syndrome	95% confidence interval	Lower limit	27.87
			Upper limit	85.33
		Standard deviation		23.137
	Epileptic seizure	Mean		47.00
		95% confidence interval	Lower limit	-181.71
			Upper limit	275.71
	Confusional syndrome	Standard deviation		25.456
		Mean		47.00
		95% confidence interval	Lower limit	27.03
	Coma and disorders of consciousness		Upper limit	66.97
		Standard deviation		23.887
		Mean		66.00
	Demyelination syndrome	95% confidence interval	Lower limit	56.10
			Upper limit	75.90
		Standard deviation		14.738
	Myasthenic syndrome	Mean		66.50
		95% confidence interval	Lower limit	-79.62
			Upper limit	212.62
	Myopathic syndrome	Standard deviation		16.263
		Mean		27.80
		95% confidence interval	Lower limit	9.35
	Neuropsychiatric symptoms		Upper limit	46.25
		Standard deviation		14.856
		Mean		51.50
	Cognitive decline	95% confidence interval	Lower limit	2.81
			Upper limit	100.19
		Standard deviation		30.600
		Mean		58.33
		95% confidence interval	Lower limit	9.63
			Upper limit	107.03
		Standard deviation		19.604
		Mean		75.42
		95% confidence interval	Lower limit	71.38
			Upper limit	79.46
		Standard deviation		6.360
		Mean		66.00
		95% confidence interval	Lower limit	37.80
			Upper limit	94.20
		Standard deviation		17.72

With regard to causal factors (Fig. 5), 18.1% of the cases with neurological symptoms arose due to medical or pharmacological error, e.g. prescription of sulpiride or its derivatives to patients with known Parkinson's disease; prolonged use (for years) of antivertigo, antiemetic and prokinetic drugs; prescribing calcium channel blockers and drugs containing magnesium to patients with myasthenia gravis; prescribing drugs without considering comorbidities

such as kidney and liver failure; overdoses due to failure to consider interactions with antiepileptic drugs listed on the information leaflet (valproic acid and lamotrigine); initial antidepressants, muscle relaxants, and opioid analgesics, and any of their combinations given in quantities other than the recommended starting doses. A statistically significant association was found between medical error as a causal factor and antivertigo/prokinetic drugs ($P = .042$), 95%

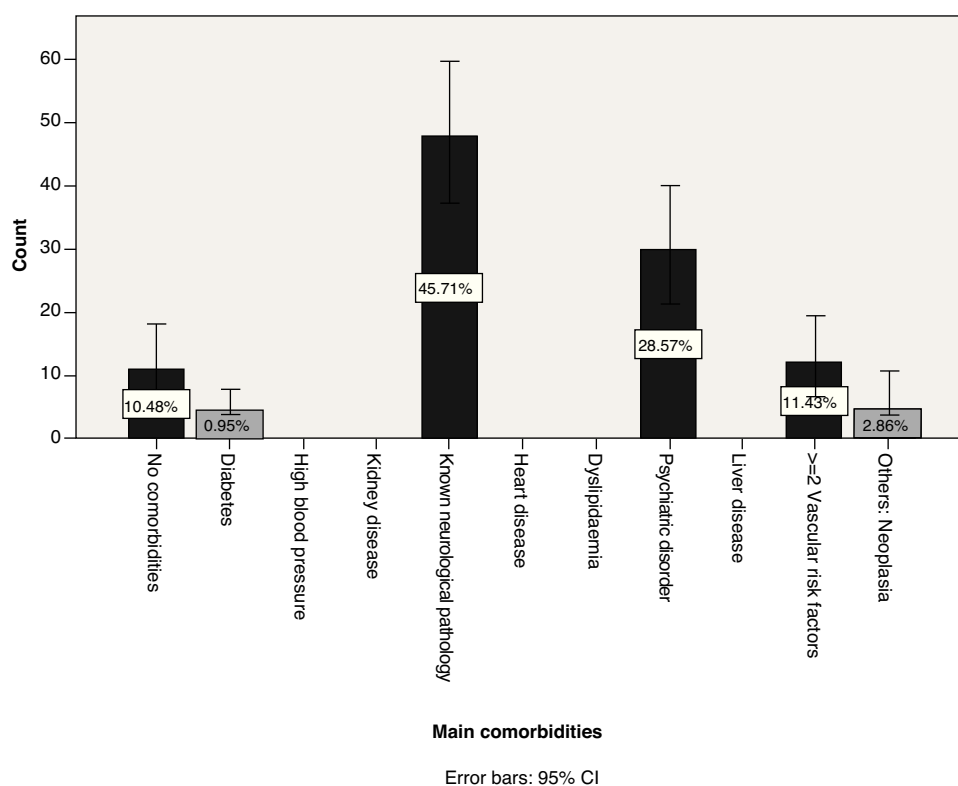


Figure 3 Count for the main comorbidities.

confidence). Of the total medical errors, 6.67% of the cases had to do with prescribing antivertigo or prokinetic drugs.

Adverse drug reactions (ADRs) accounted for 52.4% of the total (95% CI, 42.8%–61.9%); preventing such reactions is difficult. The highest percentage of patients with ADR was

found in the group with a history of psychiatric disorders, followed by patients with a history of neurological disease and patients with cardiovascular risk factors ($P = .025$). In 21.9% of the cases (95% CI, 13.9%–29.8%), effects were caused by a combination of ADR, comorbidities, and possibly also polytherapy. Many subjects in the polytherapy group were known

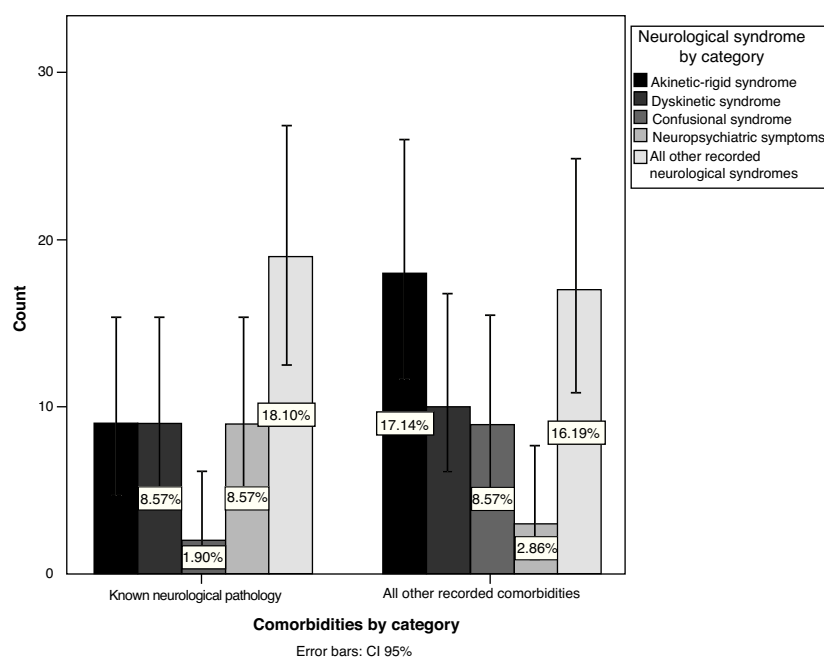


Figure 4 Counts and percentages for neurological diseases recorded as comorbidities in the main neurological syndromes observed.

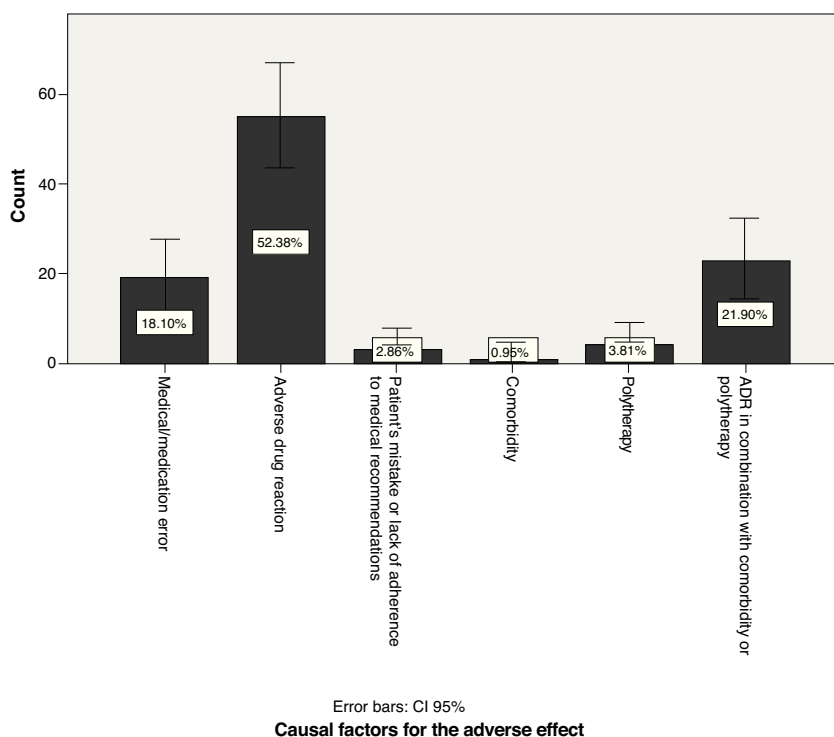


Figure 5 Count and percentages for the factors causing the adverse effect.

long-term sufferers of a neurological disease. As a result, there were more patients treated with antiparkinsonian drugs than with any other drug type ($P = .000$).

Studying the source of AEs reveals that treatment was prescribed in primary attention centres in 41% of the cases (95% CI, 31.5%–50.4%) and in specialist clinics in 59% of the cases. Only 21.9% of the cases of AE were considered preventable (95% CI, 14%–29.8%), with the remaining 78.1% being unpreventable (95% CI, 70–86%). The contingency analysis between preventability and the prescribing care level shows that primary care had the highest percentage of preventable AEs ($P = .007$) (Fig. 6).

Regarding the impact of AE, 91.4% of the patients (95% CI, 86%–96.7%) experienced a mild transient effect vs 8.6% of patients (95% CI, 3.2%–13.9%) who suffered a critical effect. These latter were patients with myasthenia gravis and drug-induced seizures due to drugs containing calcium channel blockers and magnesium; patients in status epilepticus treated with neuroleptic drugs; and semi-comatose patients treated with sedatives, analgesics, and antiepileptic drugs.

Of the patient total, 93.3% of the cases (95% CI, 88.6%–98%) required some type of care, ranging from suspension of the drug and monitoring to complementary tests, starting another treatment with a series of check-ups, or intensive care. Only 6.7% of the cases (95% CI, 1.9%–11.5%) did not require additional care. We found that the most serious adverse events occurred at the primary care level. However, the statistics did not show a link between the impact of AEs on patients and the care level ($P = .058$).

In order to evaluate the differences in the mean time to recovery from the most common entities, we performed

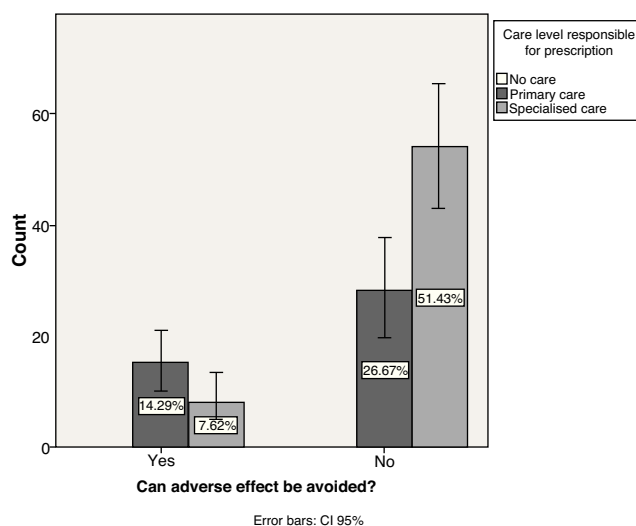


Figure 6 Percentage of preventable and unpreventable AEs, broken down by care level.

the Kruskal–Wallis test. We found statistically significant differences among the groups ($P = .038$) (Table 6).

Discussion

This is the first study to measure the frequency of exclusively neurological AEs and link them to certain drugs, comorbidities, and care levels. The overall objective is to show drains on healthcare resources arising from medical decisions and to what extent these drains can be prevented. This subject has recently been reviewed in our area.^{6,10}

Table 6 Kruskal–Wallis table. Mean resolution time for each neurological diagnosis.

Neurological diagnosis	N	Average range	Mean	95% CI	Standard deviation
<i>Period of time from prescription/suspension of the drug to recovery</i>					
Akinetic-rigid syndrome	27	57.76	185.4	90.6–280.3	239.8
Dyskinetic syndrome	17	50.85	89.2	34.5–143.9	106.3
Neuropsychiatric symptoms-confusional syndrome	21	41.55	50.05	22.34–77.76	60.8
Other determined diagnoses	28	38.38	49.8	12.6–86.9	95.8
Total	93				

According to the results of the study, the most typical characteristics in our sample were as follows: female sex, approximate age of 62 years, presence of long-term and mainly neurological comorbidities, and polypharmacy. Although the design of our study does not allow us to identify the above characteristics as risk factors, it does suggest that these subjects were more susceptible to AEs. It may therefore be advisable to use extreme precaution in such cases. Polytherapy and old age have already been described as known risk factors for ADR in general.¹⁰ The presence of akinetic-rigid, dyskinetic, neuropsychiatric, or confusional syndrome should alert doctors to the possibility of a pharmacological aetiology. This is more crucial in elderly subjects, whose mean symptom resolution time is longer and who therefore have a higher risk of chronicity. On the other hand, younger subjects experienced more idiosyncratic reactions, such as dyskinesia (mainly trembling), in conjunction with antiepileptic drugs. As the literature already indicates, doctors should take down complete and exhaustive medical histories to determine all prescriptions and their administration times.²⁴ Certain pharmacological groups should be under special supervision, given the following commonly-appearing associations: dyskinetic syndromes and antiepileptic drugs, neuropsychiatric syndrome and antiparkinsonian drugs, and akinetic-rigid syndrome and neuroleptic drugs (including antivertigo–prokinetic–antiemetic drugs). Patients with long-term neurological diseases and narrow therapeutic ranges require added precautions. This fact obliges doctors to assume the risk of higher ADR frequency when prescribing drugs. Our data support frequent revision of regular medications, cancellation of unnecessary or over-the-counter drugs, limiting administration time to the recommended period, and selecting any new prescriptions according to the type of neurological disease in this population. Based on the above, some drugs may represent a vital risk for some patients, such as those with myasthenia. In other cases, long-term treatment increases the risk of chronic and difficult to treat syndromes, such as tardive dyskinesia.

According to our observations in the group in question, the prevalence of neurological AEs was 0.586% compared to that of the initial total sample. Of this percentage, 0.12% of the cases were preventable and 0.457% were unpreventable. Given that 59% of the cases of AE were detected in out-patient clinics, and based on the total volume of patients attended, 0.36% of the cases referred to these clinics had AE. These figures seem to reflect a lower impact than that cited by prior studies, which indicated rates of neurological ADR as high as 5.1% (APEAS),²¹ with ADR accounting for 5.3%

of all hospital admissions in general.¹⁰ On the other hand, 21.9% of the AE cases were detected in hospitals. Therefore, 2.89% of the patients admitted to hospitals during the study period had AEs. These figures are similar to the ones previously described in the study which define ADR as the cause of 2.7% of all admissions to a hospital neurology department.²⁵

The low prevalence here compared to other prior articles may be due to the study design and its possible biases. As this was a hospital-level study, we only recorded data from subjects referred directly to the neurology department without including patients assessed in primary care who were not considered for referral, or subjects treated by other hospital departments (internal medicine, ICU). In all these cases, the level of suspicion of AE may have been low, especially in the presence of less-common neurological syndromes. Other possibilities to be considered are the pharmacological cause being detected and treated at the primary care level, any deaths that may have occurred, or the resolution of symptoms prior to consultation with a neurologist.

Another factor that may have contributed to the low prevalence is exclusion of patients who still presented symptoms at the end of follow-up, although the cause of the symptoms may have been drug-related. Such would be the case with tardive dyskinesias, psychotropic drug dependency, or antiarrhythmic agent consumption, as stated before.

On the other hand, our series presented a very low frequency of common neurological syndromes such as dyskinesias secondary to dopaminergic treatment in patients with parkinsonian syndromes. We think that the study design may provide another explanation. Since the above AEs are well-known to neurologists, they may have not been considered in patients already diagnosed with Parkinson's disease since there were no new motives for consultation. As a result, many of these patients would not have been selected for the study. Moreover, as the sample had a very narrow therapeutic margin, a follow-up period of 1 month might not be long enough to observe improvement after a change in treatment.

Although there were proportionally fewer cases of AE at the primary care level, these were the most critical cases. These findings make us especially mindful of the care of patients with chronic diseases and a high risk of presenting serious and potentially preventable AEs (myasthenia gravis, epilepsy, and Parkinson's disease). Concerning specialised care, most of the cases were mild, predictable, and unpreventable, but we were surprised by how difficult it was to obtain interdisciplinary agreement and identify a suspected cause of symptoms.

Lastly, our results are valuable because they enhance current knowledge and raise awareness about the possibility of neurological symptoms being associated with a specific drug. This should be considered after taking a detailed medical history and performing a thorough clinical examination. As a consequence, fewer patients would be erroneously diagnosed with a disease and doctors would not need to order complementary tests or start unnecessary treatments with their accompanying risks and consumption of resources. Our study may only show the tip of the iceberg. Other studies that compensate for our study's limitations and involve cooperation between care levels are needed in order to increase our knowledge of epidemiology, propose a specific educational approach,^{26,27} identify the safest measures, and lastly, reduce needs for care, without forgetting the impact of the diagnosis on the patient.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

- Organización Mundial de la Salud. Resolución WHA55. 18. Ginebra: Organización Mundial de la Salud; 2002.
- World Health Organization. World health alliance for patient safety, forward programme. Geneva: World Health Organization; 2004. Available from: <http://www.who.int/patientsafety/en/brochure-final.pdf> [accessed 12/2008].
- Leape LL, Berwick DM, Bate DW. What practices will most improve safety? Evidence-based medicine meets patient safety. *JAMA*. 2002;288:501–7.
- Ley 14/1986, del 25 de abril, General de Sanidad. BOE del 29 de abril de 1986.
- Ley 16/2003, del 28 de mayo, de Cohesión y Calidad del Sistema Nacional de Salud. BOE del 29 de mayo de 2003.
- Alberca R. Catástrofes neurológicas por desconocimiento y retraso diagnóstico. *Neurología*. 2010;25 Suppl. 1:52–60.
- Glick TH. The neurologist and patient safety. *Neurologist*. 2005;11:140–9.
- Glick TH, Rizzo M, Stern BJ, Feinberg DM. Neurologists for patient safety. Where we stand, time to deliver. *Neurology*. 2006;67:2119–23.
- Glick TH, Cranberg LD, Hanscom RB, Sato L. Neurologic patient safety: an in-depth study of malpractice claims. *Neurology*. 2005;65:1284–6.
- Taberner C. Neurocatástrofes farmacológicas. *Neurología*. 2010;25 Suppl. 1:68–79.
- Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med*. 1991;324:370–6.
- Thomas EJ, Studdert DM, Burstin HR, Orav EJ, Zeena T, Williams EJ, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care*. 2000;38:261–71.
- Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The quality in Australian Health-Care Study. *Med J Aust*. 1995;163:458–71.
- Vincent C, Neale G, Woloshynowych M. Adverse events in British hospitals: preliminary retrospective record review. *BMJ*. 2001;322:517–9.
- Davis P, Lay-yee R, Schug S, Briant R, Scott A, Johnson S, et al. Adverse events regional feasibility study: indicative findings. *N Z Med J*. 2001;114:203–5.
- Baker RG, Norton PG, Flintoft V, Blairs R, Brown A, Cox J, et al. The Canadian adverse study: the incidence of adverse events among hospital patients in Canada. *JAMA*. 2004;170:1678–86.
- Healey M, Shackford S, Osler T, Rogers F, Burns E. Complications in surgical patients. *Arch Surg*. 2002;137:611–8.
- Michel P, Quenon J-L, De Sarasqueta AM, Scemama O. Comparison of three epidemiological methods for estimating adverse events and preventability rates in acute care hospitals. *BMJ*. 2004;328:199–204.
- Aranaz JM, Vitaller J, Grupo de Estudio del Proyecto IDEA. Identificación de efectos adversos. De las complicaciones y efectos adversos a la gestión de los riesgos de la asistencia sanitaria. In: Estudios para la salud n.º 13. Valencia: Generalitat Valenciana; 2004. Available from: <http://www.dsp.umh.es/proyectos/idea/index.html> [accessed 12/2008].
- Estudio nacional sobre efectos adversos ligados a la hospitalización. ENEAS 2005. Ministerio de Sanidad y Consumo. Plan de Calidad para el Sistema Nacional de Salud.
- Estudio sobre la seguridad de los pacientes en atención primaria de salud. APEAS 2008. Ministerio de Sanidad y Consumo. Agencia de Calidad para el Sistema Nacional de Salud.
- Chang A, Schyve PM, Croteau RJ, O'Leary DS, Loeb JM. The JCAHO patient safety event taxonomy: a standardized terminology and classification schema for nearmisses and adverse events. *Int J Qual Health Care*. 2005;17:95–105.
- Álvarez-Soria MJ, Hernández-González A, Carrasco-García de León S, Del Real-Francia MA, Gallardo-Alcañiz MJ, López-Gómez JL. Trastornos neurológicos desmielinizantes y vacunación del papilomavirus humano. *Rev Neurol*. 2011;52:472–6.
- Nester TM, Hale LS. Effectiveness of a pharmacist-acquired medication history in promoting patient safety. *Am J Health Syst Pharm*. 2002;59:2221–5.
- Thuermann PA, Windecker R, Steffen J, Schaefer M, Tenter U, Reese E, et al. Detection of adverse drug reactions in a neurological department: comparison between intensified surveillance and a computer-assisted approach. *Drug Saf*. 2002;25:713–24.
- Nora LM, Studwell SL. Improving patients safety: what can detailed case analysis tell us? *Neurology*. 2005;65:1154–5.
- Glick TH. Evidence-guided education: patients' outcome data should influence our teaching priorities. *Acad Med*. 2005;80:147–51.