

Memory disorders associated with consumption of drugs: updating through a case/noncase study in the French Pharmacovigilance Database

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Iatrogenic amnesia is one of the main aetiologies of transient amnesia.
- Benzodiazepines and anticholinergic drugs are considered to be the drugs most often responsible for iatrogenic amnesia.
- The impact of drugs in memory disorders is particularly pronounced in elderly people, especially due to poly medication.

WHAT THIS STUDY ADDS

- An association between memory disorders and some drugs, such as benzodiazepines, antidepressants and older anticonvulsants, was found as expected.
- A strong association was found with unexpected drugs, such as benzodiazepine-like hypnotics (zopiclone and zolpidem), serotonin reuptake inhibitor antidepressants and newer anticonvulsants.
- Non-neurotropic drugs, such as isotretinoin and ciclosporin, were also associated with memory disorders.

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AIMS

To investigate putative associations of reports of memory disorders and suspected drugs.

METHODS

We used the case/noncase method in the French Pharmacovigilance Database (FPVD). Cases were reports of memory loss in the FPVD between January 2000 and December 2009. Noncases were all other reports during the same period. To assess the association between memory impairment and drug intake, we calculated an odds ratio with its 95% confidence interval.

RESULTS

Among the 188 284 adverse drug reactions recorded, we identified 519 cases of memory loss. The sex ratio was 0.6 and the median age was 54 years (range 4–93). The maximal number of cases occurred between 40–49 and 50–59 years. Evolution was favourable in 63% of the cases. We found significant odds ratios for benzodiazepines (alprazolam, bromazepam, prazepam, clonazepam etc.), benzodiazepine-like hypnotics (zolpidem and zopiclone), antidepressants (fluoxetine, paroxetine and venlafaxine), analgesics (morphine, nefopam and tramadol), anticonvulsants (topiramate, pregabalin, levetiracetam etc.), antipsychotics (aripiprazole and lithium) and other drugs, such as trihexyphenidyl, ciclosporin and isotretinoin.

CONCLUSIONS

Our study confirmed an association between memory disorders and some drugs, such as benzodiazepines and anticonvulsants. However, other drugs, such as benzodiazepine-like hypnotics, newer anticonvulsants, serotonin reuptake inhibitor antidepressants, isotretinoin and ciclosporin were significantly associated with memory disorders, although this was not described or poorly described in the literature.

Taking account of the limits of this study in the FPVD (under-reporting, notoriety bias etc.), the case/noncase method allows assessment and detection of associations between exposure to drugs and a specific adverse drug reaction, such as memory disorders, and could thus generate signals and orientate us to further prospective studies to confirm such associations.

Introduction

Memory is defined as the ability to store, retain and recall information. The human memory system is divided into the following three components: short-term memory, allowing recall for a period of several seconds to 1 min without rehearsal (one form is working memory); long-term explicit memory, concerning facts taken out of context (semantic memory) and concerning information specific to a particular context, such as time and place (episodic memory); and finally, implicit memory or procedural memory, based on implicit learning.

Every stages of the process of memorization and all of the different components of memory can be affected in an isolated way or in association. Among the different patterns of memory disorders, the following two main forms of amnesia can be isolated: anterograde amnesia, when the subject cannot memorize new information; and retrograde amnesia, when the subject is unable to recall events occurred before the injury.

Amnesia can also be subdivided into long-term amnesia and short-term (or transient) amnesia. Concerning transient amnesia, the main aetiologies are idiopathic transient global amnesia, epileptic, vascular, psychogenic and iatrogenic amnesia [1]. Traditionally, it is considered that benzodiazepines and anticholinergic drugs are mainly responsible for this last form [2].

The impact of drugs on memory disorders is particularly pronounced in elderly people because of poly medication. It is established that there is a decrease of mnemonic abilities with ageing, but iatrogenic responsibility may be evoked when a memory alteration occurs suddenly and/or recently in an elderly person without other symptoms of dementia. The action of drugs on memory is more or less specific and serious depending on the memory system affected. Thus, analysis of the type of memory alteration can be used to incriminate more a particular drug during poly medication.

The aim of this study was to investigate the putative association of reports of memory disorders (without dementia) and suspected drugs, using the case/noncase method in the French Pharmacovigilance Database (FPVD).

Methods

Case/noncase method

The case/noncase method measures the disproportionality of combination between a drug and a particular adverse drug report (ADR) in a pharmacovigilance database [3–6]. This method can be used to generate signals from a pharmacovigilance database. Cases are defined as reports of the ADR of interest and noncases as all other reports of ADR.

For each drug of interest, the association with the ADR was assessed by calculating an ADR reporting odds ratio (ROR) with its 95% confidence interval (CI).

Selection of cases and noncases

Since 1985, all ADR reports sent spontaneously by health professionals to one of the 31 French Regional Centres of Pharmacovigilance have been entered into the FPVD.

In our study, we collected ADRs recorded in the FPVD between 1 January 2000 and 31 December 2009.

Cases were defined as HLT (High Level Term, MedDRA 11.0, Medical Dictionary for Regulatory Activities) 'memory loss (dementia excluded)', including 'amnesia', 'anterograde amnesia', 'global amnesia', 'memory disturbance' and 'amnesic disorder'. Noncases, using as controls, were all the remaining ADR reports recorded in the database during the same period.

Drug exposition was defined by the presence in the report of the drug checked 'suspect' according to the World Health Organization criteria, whatever the level of causality assessment. We selected drugs for which four or more reports of memory disorders had been registered in the FPVD.

If available, the following data were also collected from each report: age, sex, seriousness and evolution of the ADR.

Seriousness was defined as an ADR leading to hospitalization (or prolongation of hospitalization), persistent or significant disability or incapacity, life threatening or death.

Statistical analysis

Collected data were compared between reports defined as memory disorders (cases) and all other reports in the database (noncases). We calculated an ROR to compare risk of exposure to different drugs in cases and noncases. The RORs are given with their 95% CIs [7].

Results

Of the 188 284 reports recorded in the French Pharmacovigilance database during the studied period, we identified 519 cases of memory loss (dementia excluded), representing 0.3% of all reports. Unfortunately, the type of memory affected was often not specified. Among them, 292 (57%) were observed in women (sex ratio 0.6). Median age was 54 years (range 4–93 years).

The maximal number of cases occurred between 40–49 and 50–59 years ($n = 98$ and $n = 96$, respectively; Figure 1). In addition, 127 cases were reported after 70 years (74 after 75 years; Figure 1).

Most cases (60%) were considered as 'nonserious'. None of the cases induced irreversible damage. For the majority of the patients, symptoms resolved after withdrawal of the suspect drug (63% of the cases).

Among the 519 cases, 301 drugs were mentioned as suspect. The main therapeutic classes suspected were hyp-

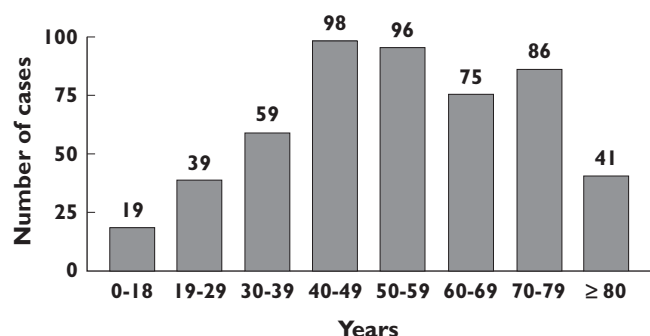


Figure 1

Repartition of the 519 cases of memory disorders according to age

notics (76 cases), anticonvulsants (68 cases), anxiolytics (66 cases), antidepressants (55 cases), analgesics (45 cases) and antipsychotic drugs (29 cases).

Significant RORs were found for 30 drugs mentioned in Table 1. Among these drugs, zolpidem [ROR 23.9, 95% CI (17.9, 31.9)], topiramate [ROR 11.6, 95% CI (6.3, 11.3)], zopiclone [ROR 8.7, 95% CI (5.2, 14.3)], alprazolam [ROR 8.0, 95% CI (4.7, 13.7)] and bromazepam [ROR 7.6, 95% CI (4.4, 13.0)] presented the most significant associations with memory disorders.

Discussion

The aim of this work was to assess which drugs could be implicated in the occurrence of memory disorders through a case/noncase study in the FPVD.

Preclinical data are often limited and clinical trials, although essential, are performed on a too small number of patients for detecting uncommon effects. Thus, the case/noncase method is a very useful method for assessing and detecting associations between a specific adverse drug effect and exposure to drugs in real conditions of use, because it is simple and quick and the data used are already available. Several studies have been recently published using this method on this database applying to different fields of drug safety [3,8] but also to pharmacodependence [9].

The limits of this methodology in the FPVD lie especially in the under-reporting of ADRs in general, and particularly in elderly people, and notoriety bias. Indeed, the association between a drug and an adverse drug effect could be decreased if another effect is more often reported by physicians, and vice versa. Despite these inherent limits of this type of study, case/noncase methodology is very useful to generate signals, especially in pharmacovigilance.

In the FPVD, 519 cases of memory disorders were reported in the last 10 years. The type of memory affected could not be analysed because this information was often

not described. The median age was 54 years and, surprisingly, only 17% of cases were older than 75 years, indicating that age is not the most important associated factor in drug-induced amnesia. However, in elderly people, the iatrogenic responsibility for the occurrence of amnesia is difficult to determine because of the presence of other aetiologies, such as incipient dementia and depression. Consequently, this ADR is probably under-reported in this age category.

Memory disorders were reported mostly in women in the FPVD between 1 January 2000 and 31 December 2009 (57%). However, we also observed that women presented ADRs more often in the FPVD during the same period (54%).

Concerning drugs involved in memory disturbance, positive associations were found with some expected drugs, such as benzodiazepines, tricyclic antidepressants or antipsychotics, but also with unexpected drugs, such as benzodiazepine-like hypnotics, serotonin reuptake inhibitors (SRIs) antidepressants and second-generation anticonvulsants. Overall, six main therapeutic classes were mainly associated with memory alterations.

The most represented class was the benzodiazepines (82 cases), in particular, alprazolam, bromazepam, clonazepam, lorazepam, prazepam and tetrazepam. In these cases, after analysis of the clinical description in the database, we frequently retrieved anterograde amnesia, which is a well-known effect with this pharmacological class; indeed, it was mentioned in the summary of product characteristics as a potentially dose-dependent effect. Moreover, in the literature, these effects are often described with short-acting benzodiazepines [10], and the mechanism underlying the effects involves the ω_1 subtype of GABA_A receptors [11, 12].

We also observed a possible association with the benzodiazepine-like hypnotics, zolpidem and zopiclone. Interestingly, zolpidem presented the most important association with memory disorders [ROR 23.9, 95% CI (17.2, 31.9)]. The effects of zolpidem on memory are at the moment controversial. Some authors consider that this molecule can induce similar amnesic effects to benzodiazepines [13], whereas others [14] consider it to be safer than benzodiazepines. The fact that zolpidem had the most important association with amnesia could be explained by its mechanism of action. Indeed, zolpidem has a great affinity for ω_1 subtype receptors which, as mentioned earlier, are implicated in memory defects. In contrast, zopiclone presents affinity not only for the ω_1 subtype receptors but also for the ω_2 subtype, underlying its anxiolytic properties in humans [15, 16] and anticonvulsant, myorelaxant and anxiolytic properties in animals [17]. Thus, zopiclone induces memory disorders to the same extent as benzodiazepines [18, 19].

Antidepressants were also well represented in our study. Although we did not show significant associations with memory disorders, and memory disorders were not mentioned in the summary of product characteristics of

Table 1

Risk of exposure to drugs and occurrence of memory disorders in the French Pharmacovigilance Database (FPVD)

Drugs	Number of ADRs in the FPVD	Number of memory disorders in the FPVD	Mention in French Summary of Product Characteristics	Reporting odds ratio (95% confidence interval)	P-value
Benzodiazepines (anxiolytics or not)		82			
Alprazolam	664	14	Anterograde amnesia (risk increasing with dosage)	8.0 (4.7, 13.7)	<0.001
Bromazepam	697	14		7.6 (4.4, 13.0)	<0.001
Clonazepam	900	17		7.2 (4.4, 11.7)	<0.001
Lorazepam	387	7		6.8 (3.2, 14.4)	<0.001
Prazepam	305	6		7.3 (3.3, 16.5)	<0.001
Tetrazepam	770	5		2.4 (1.0, 5.8)	<0.05
Other anxiolytics		12			
Hydroxyzine	717	6	No data	3.1 (1.4, 6.9)	<0.01
Meprobamate	630	6	No data	3.5 (1.6, 7.9)	<0.01
Benzodiazepine-like hypnotics		76			
Zolpidem	963	54	Anterograde amnesia (risk increasing with dosage)	23.9 (17.9,31.9)	<0.001
Zopiclone	703	16		8.7 (5.2, 14.3)	<0.001
Antidepressants		55			
Selective serotonin reuptake inhibitors		30			
Fluoxetine	932	9	No data	3.6 (1.8, 6.9)	<0.001
Paroxetine	1831	16	No data	3.3 (2.0, 5.4)	<0.001
Others		14			
Venlafaxine	1145	7	No data	2.2 (1.0, 4.6)	<0.05
Antipsychotic		25			
Aripiprazole	234	4	No data	6.3 (2.3, 17.1)	<0.001
Mood stabilizer		4			
Lithium	450	4	No data	3.3 (1.2, 8.8)	<0.05
Anticonvulsants		68			
Gabapentin	628	5	Frequent: amnesia	2.9 (1.2, 7.1)	<0.05
Lamotrigine	658	5	No data	2.8 (1.2, 6.8)	<0.05
Levetiracetam	388	4	Frequent: amnesia	3.8 (1.4, 10.2)	<0.01
Pregabalin	567	7	Frequent: memory disorders	4.6 (2.2, 9.7)	<0.001
Topiramate	361	11	Frequent: memory disorders, amnesia	11.6 (6.3, 11.3)	<0.001
Valproic acid/valproate	1732	12	Rare: cognitive disorders	2.6 (1.4, 4.6)	<0.001
Analgesics		45			
Morphine	751	6	No data	2.9 (1.3, 6.9)	<0.01
Nefopam	520	4	No data	2.8 (1.1, 7.6)	<0.05
Tramadol	2463	12	No data	1.8 (1.0, 3.2)	<0.05
Others					
Bupropion	568	7	Rare: memory disorders	4.6 (2.2, 9.7)	<0.001
Ciclosporin	547	4	No data	2.7 (1.0, 7.2)	<0.05
Hepatitis B vaccine	1965	31	No data	6.1 (4.2, 8.8)	<0.001
Isotretinoin	553	4	No data	2.7 (1.0, 7.1)	<0.05
Mefloquine	247	4	Memory disorders	6.0 (2.2, 16.2)	<0.001
Trihexyphenidyl	201	4	No data	7.4 (2.7, 20.0)	<0.001

these drugs, tricyclic antidepressants are well described as able to induce these disturbances, at least in part through their atropinic properties [20]. It is now clear that some of the adverse effects produced by many tricyclic antidepressants are a consequence of their blockade of muscarinic cholinergic receptors, which are the dominant cholinergic receptors in the brain and seem to be involved in learning and memory. Among tricyclic antidepressants, amitriptyline tends to produce atropinic adverse effects more frequently [21–24]. However, surprisingly, in our study, no tricyclic antidepressant was found to be significantly asso-

ciated with a memory disorder. One hypothesis is that this could be linked to a notoriety bias. Indeed, as effects on memory are well known with these drugs owing to their atropinic properties, physicians do not report them to their regional centres of pharmacovigilance. Moreover, these drugs are now less prescribed, especially in elderly people.

Conversely, in this class of antidepressants we identified associations between memory disorders and some SRIs, such as fluoxetine and paroxetine. These antidepressants share a common characteristic, their selective blockade of the reuptake of serotonin (5-HT) [21, 25, 26]. The

principal advantages of these drugs are that they are safer and better tolerated than tricyclic antidepressants [27]. However, SRI antidepressants have several other properties, including inhibition of noradrenaline reuptake, inhibition of dopamine reuptake, a 5HT_{2c} receptor agonist effect, a muscarinic antagonist effect, effects on sigma receptors, inhibition of nitric oxide synthase and inhibition of cytochromes P450 2D6, 3A4 and 1A2. For example, paroxetine has a muscarinic antagonist effect [27], which could explain its amnesic effects observed in this study. Moreover, memory disorders could be due to their serotonergic effects, because several studies indicate that serotonergic neurons could play a significant role in learning and memory [28–30]. Injections of drugs with serotonergic properties in animals induce disturbances in memory functions [31–33], but the precise nature of this regulation remains unclear. Some authors suggest that serotonergic and cholinergic systems interact in a complex manner in the regulation of learning and memory functions [34, 35]. Conversely, although associated with memory dysfunctions in the present study, it has been shown that fluoxetine, which has no atropinic effects, could lead to positive effects on memory by counteracting the memory impairment produced by other agents, especially in rats [36–38].

In the same way, another antidepressant, venlafaxine, a noradrenaline and serotonin reuptake inhibitor, was also associated with memory disorders in our study. However, this drug has not been shown to have a significant affinity for muscarinic cholinergic receptors and does not seem to exert the stimulant effect on memory seen with fluoxetine [21].

In the pharmacological class of antipsychotics, only one drug, aripiprazole, was identified as being associated with memory disorders, although there are many drugs in this class with atropinic properties. As for tricyclic antidepressants, we hypothesized an under-reporting owing to the knowledge by the physicians of the atropinic properties of these drugs and thus their ability to induce memory disorders. For aripiprazole, we did not find any report of memory trouble mentioned in the literature.

Lithium was also associated with memory disorders in this study. The effects of this drug on cognition have been well described, in particular, delirium and impaired memory and psychomotor performance [39, 40].

Anticonvulsants were also reported in our study to be associated with amnesic effects. Six drugs were identified; one 'older' anticonvulsant (valproate/valproic acid) and five newer drugs (lamotrigine, levetiracetam, gabapentin, pregabalin and topiramate). In the context of epilepsy, it is difficult to assess the involvement of drugs in the occurrence of amnesic effects, because of the multifactorial pattern of the pathology. Cognitive disorders induced by anticonvulsants seem to be different in children, adults and elderly people. Polymedication with several anticonvulsants could also increase the risk of memory disorders

[41]. Some authors reported that valproic acid does not alter memory function [42]. In other studies conducted in non-elderly people, phenobarbital and primidone appeared to have more cognitive effects than carbamazepine, phenytoin and valproic acid [43, 44]. Newer anticonvulsants seem to have less cognitive effects than older ones [45], but only a few studies have been conducted in monotherapy. Among them, topiramate presented a strong association with memory disorders [ROR 11.6, CI (6.3, 11.3)]. These effects are well known with this drug [46, 47], which especially alters short-term memory [48]. Levetiracetam could also induce memory disorders, because it is reported in the summary of product characteristics. Conversely, in the literature, levetiracetam is considered as inducing minor effects on cognition [46, 49]. However, manufacturing data reported that 2% of levetiracetam-treated patients experienced amnesia compared with 1% of placebo-treated patients in randomized, double-blind, placebo-controlled studies.

An increase of the incidence of memory disorders was also associated with pregabalin use. This drug is mentioned in particular in a publication reporting cases of treated patients which manifested partial significant impairments in episodic memory of verbal and visual information [50].

We found mention of amnesia with gabapentin and lamotrigine only in clinical trials (manufacturing data), although it is mentioned in the summary of product characteristics for gabapentin.

The last main pharmacological class of drugs associated with memory disorders in our study is analgesics, including morphine, nefopam and tramadol. In contrast to our results, in a study assessing cognitive effects of different analgesics, it has been shown that morphine could increase cognitive performances of healthy subjects aged from 25 to 40 years [51]. Concerning nefopam and tramadol, no data are available in the literature about their potentially amnesic properties. However, it is known that nefopam presented atropinic properties (summary of product characteristics). Thus, these properties could explain the memory disorders observed.

Among the other drugs with a positive association, we found mefloquine, an antimalarial drug for which one case of memory disorders has been described, but the causative role of the drug is discussed; moreover, the importance of a differential diagnosis of neuropsychiatric disorders from toxic or parasitic origins was underlined [52].

For isotretinoin, hepatitis B vaccine and ciclosporin, no previous cases of memory disturbance have been reported to our knowledge. In our study, for all the cases associated with isotretinoin administration, imputability, a causality assessment score, was evaluated as possible (I1), according to the official French methodology [53], excepted for one in which imputability was plausible (I2). However, for two cases, after isotretinoin discontinuation, patients completely recovered.

In the same way, the responsibility of ciclosporin for memory disorders was judged as possible in three of the four cases reported. For the fourth case, imputability was plausible; the subject developed paraesthesia, dysarthria, tremor, amnesia and faintness nearly 7 months after initiation of treatment with ciclosporin. These effects resolved spontaneously 2 months after drug withdrawal.

Finally, for hepatitis B vaccine, most of the cases of memory disorders were accompanied by other adverse effects, and the responsibility of the vaccine in the occurrence of memory disorders was often discussed.

In conclusion, taking into account the limits of the methodology, this study confirmed the association of memory disorders with drugs such as benzodiazepine and older anticonvulsants and, interestingly, showed a strong association with other drugs, such as benzodiazepine-like hypnotics, SRI antidepressants and newer anticonvulsants. Moreover, we found positive associations with non-neurotropic drugs, such as isotretinoin and ciclosporin, which merit exploration. All these data should be confirmed with prospective studies, and we encourage physicians to notify memory disorders, especially in elderly people.

Competing Interests

There are no competing interests to declare.

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