

Drug-induced hallucination: A case/non case study in the French Pharmacovigilance Database

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ABSTRACT – Background and Objectives: Hallucinations are sensory perceptions which occur without external stimuli. There are associated with psychiatric disease but also can be related to organic disease and drug or toxic exposure. The purpose of our study was to investigate the association between exposure to medications and the reporting of hallucinations using data from the spontaneous-reporting French Pharmacovigilance Database (FPVD).

Methods: We used the case/noncase method in the FPVD. Cases were all the observations of hallucination with the LLT term “perception disturbances”, registered into the FPVD from January 1985 to Jan 2013. Data were expressed as odds ratio (OR) with their 95% confidence intervals.

Results: Among the 469,181 reports of adverse effects recorded between 1985 and 2013, 4,086 are hallucinations. For about 50% of these hallucinations were experimented by patient older than 65 years old.

A statistically significant OR was found with several medications included rasagiline (OR 17.6 [95%CI 10.4-29.8]), zolpidem (OR 12.9 [95%CI 11.3-14.8]), methylphenidate (OR 9.3 [95%CI 5.9-14.6]) and baclofene (OR 5.4 [95%CI 3.7-7.8]). An increased risk of hallucinations was also observed with non central nervous system drugs, including ertapenem (OR 24.0 [95%CI 14.2-40.5]), voriconazole (OR 12.9[95%CI 10.2-16.5]) and valacyclovir (OR 9.1 [95%CI 6.9-11. 9]).

Conclusions: This pharmacoepidemiological study describes an association between drugs and hallucinations. This relationship involves not only some already suspected drugs but also other drugs less known to induce such an adverse reaction. Despite the mandatory limits of this kind of study, these data should lead to special precautions in patient at risk.

Introduction

In 1837 the French alienist Esquirol defined hallucinations as follows. “A person is said to labor under a hallucination, *or to be a visionary*, who has a thorough conviction of the perception of a sensation, when no external object, suited to excite this sensation, has impressed the senses”^{1,2}.

Hallucination is now defined by the Diagnostic and Statistical Manual of Mental Disorders DSMV as “a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation of the relevant sensory organ”³.

It is a relatively common symptom, with a prevalence of 4 to 38%⁴. The percentage of “normal” subjects reporting hallucinatory experiences is substantial^{5,6}. They may be symptomatic of cerebral disease, functional psychoses and can also be induced or worsened by drugs⁷.

In this context, the aim of this study was to investigate the association between exposure to medications and hallucinations.

Methods

The study used data from the French Pharmacovigilance Database (FPVD) of all adverse reactions occurring with commercially approved drugs in France. This database was established in 1985⁸ to register all adverse drug reactions (ADR) reported by health professionals or patients to the French Pharmacovigilance System. Reports are reviewed and analyzed by medically qualified personnel before being entered into the FPVD.

ADR were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®)⁹.

Observations reported with hallucination from 1985 to 1 Jan 2013 were reviewed.

The case/non-case method was used to measure disproportionality of the combination between a drug and a particular ADR in the FPVD. Cases were defined as reports corresponding to hallucination from the LLT terms “perception disturbances”, and non-cases as all other reported ADRs for the same period. Data in the FPVD are anonymous. The odds ratio (OR) is the ratio of reporting of one specific event versus all other events for a given drug compound¹⁰. The 95% confidence intervals (CI) were calculated using the Woolf method¹¹.

Results

469,181 reports of ADRs had been recorded in the FPVD from 1985 to 1 January 2013. 4086 patients experienced hallucinations. The average age was 59.8 years (\pm 28.4). 53% were older than 65 years old and 9 % were children of less than 15 years. The sex ratio (female/male) was 1.3. ADR are serious in 1691 cases (41%).

Underlying disease that can potentially induce hallucination is specified in 592 cases (14%): 510 patients (12%) had psychiatric history, 76 history of dementia and 6 history of Lewy body dementia. Hallucination is associated with other adverse event known to induce this symptom in 167 cases (4%): 80 drug interactions, 35 withdrawal medication (opioid, benzodiazepine, antidepressant, neuroleptic and baclofen), 19 hyponatraemia (proton pump inhibitors, antidepressant, desmopressin and diuretic), 15 encephalopathy, 9 cerebellous syndrome, 7 anticholinergic syndrome and 2 hypoglycemia.

The type of hallucination is mainly unspecified (69%), visual (24%) or auditory

(6%). Patients recovered in 83%. Two patients died after responding inappropriately to hallucinations (one fall and one suicide). For the remaining cases, the outcome is unknown (7%), the patient is not yet restored (8%) or is recovering (about 2%).

Overall, a total of 4231 reported medications are suspected, a single one in 3298 cases (81%) and more than one in 19%. The onset delay of ADR was less than one month after initiation of the medication in 22% and in less than two days in 8%. In 5 cases, the ADR was immediate including 3 hallucinations after diazepam injection. Administration was mainly oral (82%).

The most important occurrences are zolpidem (n = 250), tramadol (n = 240), levodopa (n = 212), morphine (n = 143), ofloxacin (n = 120), trihexyphenidyle (n = 107), ciprofloxacin (n = 105), piribedil (n = 81), oxybutynine (n = 86), omeprazole (n = 76) and voriconazole (n = 74).

The highest significant OR is for ertapenem, lisuride, entacapone, selegiline and trihexyphenidyle (Table 1). In the top ten, we find two medications used in non-neurological or psychiatric indications: ertapenem and oxybutynine.

Parkinson disease therapy was mainly implicated with 408 cases (Table 2a). Benzodi-

Table 1
Top ten of statistically significant OR for the association between medication and hallucinations in the FPVD*.

Drug	OR (95% CI)
Ertapenem	24.0 (14.2-40.5)
Lisuride	23.1 (13.5-39.6)
Entacapone	20.4 (12.8-32.4)
Selegiline	19.2 (12.9-28.7)
Trihexyphenidyle	17.8 (14.5-21.9)
Scopolamine	17.7 (11.9-26.2)
Pramipexole	17.7 (11.8-26.5)
Rasagiline	17.6 (10.4-29.8)
Levodopa + carbidopa	17.2 (12.9-22.8)
Oxybutynine	16.6 (13.2-20.8)

* 95% CI calculated using Woolf's method, OR = odd ratio, CI = confidence interval, FPVD = French Pharmacovigilance Database.

azepines and benzodiazepine-like therapies were also well-represented (n = 365) including 250 cases with zolpidem (Table 2b). Opioids were involved in many cases and mainly tramadol (n = 240) (Table 2c). Other anticholinergic medications induced hallucinations as antidepressants (duloxetine...), anxiolytics (hydroxyzine...), neuroleptic (aripiprazole...),

antihistaminics therapies (promethazine, mequitazine), overbladder therapies (oxybutynine, trospium), treatment of the neuroleptic-induced parkinsonism (trihexyphenidyle) and analgesic (nefopam) (Table 2d, 2e). Other drugs with nervous central system activities produced also hallucination with significant OR including antiepileptic (gabapentine,

Table 2
 CNS medications with statistically significant OR for the association with hallucination in the FPVD*.

Drug	Hallucination	All reports FPVD	OR (95% CI)
a-Parkinson disease therapy			
Bromocriptine	91	902	13.0 (10.5-16.2)
Entacapone	21	139	20.4 (12.8-32.4)
Levodopa + carbidopa	56	432	17.2 (12.9-22.8)
Levodopa + benserazide	138	1171	15.7 (13.1-18.8)
Levodopa, entacapone, carbidopa	18	149	15.7 (9.6-25.7)
Lisuride	16	95	23.1 (13.5-39.6)
Pergolide	16	192	10.4 (6.2-17.3)
Piribedil	81	699	15.2 (12.0-19.2)
Pramipexole	27	202	17.7 (11.8-26.5)
Rasagiline	16	120	17.6 (10.4-29.8)
Selegiline	28	195	19.2 (12.9-28.7)
Trihexyphenidyle	107	808	17.8 (14.5-21.9)
Tropatepine	29	596	5.9 (4.0-8.5)
b-Benzodiazepine and benzodiazepine-like therapies			
Bromazepam	37	2863	1.5 (1.1-2.1)
Clonazepam	37	1907	2.3 (1.6-3.1)
Lorazepam	34	1680	2.4 (1.7-3.3)
Oxazepam	26	1418	2.1 (1.4-3.1)
Triazolam	12	370	3.8 (2.1-6.8)
Zolpidem	250	2586	12.9 (11.3-14.8)
Zopiclone	74	1942	4.6 (3.6-5.8)
c-Opioids therapies			
Buprenorphine	38	1946	2.3 (1.7-3.1)
Dextromethorphan	11	276	4.7 (2.6-8.7)
Morphine	143	3939	4.4 (3.7-5.2)
Nalbuphine	15	301	6.0 (3.6-10.1)
Opium	14	604	2.7 (1.6-4.6)
Oxycodone	21	334	7.7 (4.9-11.9)
Tramadol	240	4784	6.3 (5.5-7.2)
d-Antidepressants, anxiolytics and neuroleptics			
Agomelatine	7	227	3.6 (1.7-7.7)
Amitriptyline	52	1864	3.3 (2.5-4.3)
Aripiprazole	10	502	2.3 (1.2-4.3)
Citalopram	26	1438	2.1 (1.4-3.1)
Clomipramine	46	2256	2.4 (1.8-3.2)

* 95% CI calculated using Woolf's method, OR = odd ratio, CI = confidence interval, FPVD = French Pharmacovigilance Database.

Table 2
CNS medications with statistically significant OR for the association with hallucination in the FPVD*
(continuation).

Drug	Hallucination	All reports FPVD	OR (95% CI)
d-Antidepressants, anxiolytics and neuroleptics			
Duloxetine	21	496	5.1 (3.3-7.8)
Fluvoxamine	17	749	2.6 (1.6-4.3)
Haloperidol	30	2139	1.6 (1.1-2.3)
Hydroxyzine	45	1828	2.9 (2.1-3.9)
Paroxetine	57	3405	2.0 (1.5-2.5)
Sertraline	22	1116	2.3 (1.5-3.5)
Venlafaxine	28	1891	1.7 (1.2-2.5)
e-Other medications with anticholinergic activity			
Atropine	42	820	6.2 (4.5-8.5)
Butylscopolamine	3	43	8.5 (2.6-27.6)
Mequitazine	18	286	7.7 (4.8-12.4)
Nefopam	70	981	8.9 (6.9-11.3)
Oxybutynine	86	689	16.6 (13.2-20.8)
Piperazine	2	39	6.2 (1.5-25.5)
Promethazine	14	315	5.3 (3.1-9.1)
Pseudoephedrine chlorhydrate	9	140	7.8 (4.0-15.4)
Scopolamine	29	217	17.7 (11.9-26.2)
Trospium chloride	7	108	7.9 (3.7-17.0)
f-Other CNS therapies			
Baclofene	30	665	5.4 (3.7-7.8)
Buflomedil	15	843	2.1 (1.2-3.4)
Clobutinol	13	289	5.4 (3.1-9.4)
Donepezil	18	775	2.7 (1.7-4.3)
Gabapentine	22	886	2.9 (1.9-4.4)
Galantamine	7	328	2.5 (1.2-5.3)
Ketamine	14	554	3.0 (1.7-5.0)
Leviracetam	28	835	4.0 (2.7-5.8)
Memantine	16	442	4.3 (2.6-7.1)
Methylphenidate	20	267	9.3 (5.9-14.6)
Modafinil	6	123	5.8 (2.6-13.3)
Oxetorone	4	129	3.6 (1.3-9.9)
Pregabalin	32	1176	3.2 (2.2-4.6)
Sodium 4-hydroxybutyrate	11	97	14.6 (7.8-27.4)
Topiramate	17	609	3.3 (2.0-5.3)
Varenicline	9	521	2.0 (1.0-3.9)

* 95% CI calculated using Woolf's method, OR = odd ratio, CI = confidence interval, FPVD = French Pharmacovigilance Database.

leviracetam, pregabalin and topiramate), Alzheimer therapies (donepezil, galantamine, memantine), migraine treatment (oxetorone), analgesic (ketamine), hyperactivity disorder and/or narcolepsia treatment (methylphenidate, modafinil, sodium-4-hydroxybutyrate), an antispastic treatment (baclofen) and an antitussive therapy (clobutinol) (Table 2f).

An increased risk of hallucinations was also observed with non central nervous system (NCNS) drugs (Table 3), including ertapenem, voriconazole, valacyclovir, oseltamivir, mefloquine, ciprofloxacin and omeprazole. Other drug presented less important OR but statistically significant: tacrolimus and prednisolone.

Table 3
Description of cases with statistically significant odds ratio (ORs) for the association between NCNS medication and hallucination in the FPVD*.

Drug	All reports FPVD	Hallucination cases (n)	Sex ratio (F/H)	Mean age (y)	OR (95% CI)
Aciclovir	2045	38	1.6	58.4	4.0 (2.9-5.6)
Ciprofloxacin	3342	105	0.7	66.6	3.8 (3.1-4.6)
Efavirenz	2337	35	0.35	42.2	1.7 (1.2-2.4)
Ertapenem	98	17	0.7	73.8	24.0 (14.2-40.5)
Ivabradine	100	3	0	83	3.5 (1.1-11.1)
Levofloxacin	1610	49	0.9	74.8	3.6 (2.7-4.8)
Mefloquine	801	40	1.2	32.5	6.0 (4.4-8.3)
Metoprolol	408	9	1.25	59.7	2.6 (1.3-5.0)
Montelukast	322	9	0.8	19.2	3.2 (1.7-6.4)
Moxifloxacin	623	12	1.4	72.5	2.2 (1.3-3.9)
Norfloxacin	1593	37	5.7	68.6	2.7 (1.9-3.8)
Ofloxacin	3923	120	1.2	62.9	3.7 (3.1-4.4)
Omeprazole	4423	76	0.92	69.0	2.0 (1.6-2.5)
Oseltamivir	258	16	1.1	30.8	7.5 (4.5-12.5)
Pantoprazole	1284	21	1.3	73.1	1.9 (1.2-2.9)
Piperacilline+tazobactam	793	14	1.8	74.1	2.0 (1.2-3.5)
Proguanil	802	13	1.2	41	1.9 (1.1-3.2)
Valacyclovir	806	56	1.4	76.8	9.1 (6.9-11.9)
Voriconazole	735	74	0.48	56.2	12.9 (10.2-16.5)

* 95% CI calculated using Woolf's method, OR = odd ratio, CI = confidence interval, NCNS = non central nervous system, FPVD = French Pharmacovigilance Database.

Discussion

It is sometimes difficult to establish if hallucination is caused by a drug or by an underlying illness. Indeed, hallucinations are also frequent in schizophrenia and related psychotic disorders.

Our study shows that there is an increased risk of reporting of hallucination, during treatment with several medications. They have sometimes but not always a known nervous central system activity. Several cases of drug-induced hallucination are published but to the best of our knowledge, this is the first review of drug-induced hallucination based on a large pharmacoepidemiological study.

Hallucinations will normally resolve after withdrawal of the causative drug.

The elderly, and those with a previous history of psychiatric illness, are at increased risk of drug-induced hallucination. Hallucinations caused by drugs are commonly visual but in our study the type is mainly unspecified in the coding.

Several differential diagnoses have to be taken into account: in more severe cases of syndrome of inappropriate secretion of antidiuretic hormone or hyponatraemia, anticholinergic syndrome, serotonin syndrome¹² as auditory and visual hallucinations are included in Sternbach's diagnostic criteria. Hallucinations can also appear after SRI discontinuation¹³. However, some types of visual hallucination in Charles Bonnet syndrome (CBS) have been treated with SRI¹⁴ and CBS is a condition characterized by visual hallucinations in cognitively normal patients with acquired vision loss. Drug-induced hallucinations in healthy elderly subjects should also be investigated as possible predictive marker of Lewy body disease (DLB). It is then very important to have a sufficient accuracy in the

data when analyzing those observations and more than all when treating those patients.

Zolpidem is the more frequent medication suspected in hallucination but fluoroquinolones represent also an important class. Neuropsychiatric symptoms are common also in Parkinson's disease (PD) but the other common cause is the use of dopaminergic drugs. Aggravation of psychosis with hallucinations is described also with neuroleptic drugs maybe because of their antimuscarinic properties.

Actually, drug-induced hallucinations most often reflect anticholinergic properties. There are several anticholinergic drugs, some are structurally related to atropine. Their ability to cause vivid and sometimes exotic hallucinations is well-known and has led to their misuse. Nefopam is a centrally acting non-opioid analgesic. It should be used with caution in the elderly and in conjunction with other drugs that have anticholinergic activity. Antimuscarinic therapy for overactive bladder¹⁵ as oxybutynin like other drugs used in urology produces anticholinergic symptoms and overdoses causes hallucinations. Solifenacin, which is a more recent, can induce also hallucination but only one case has been reported in our study¹⁵. First generation H1-antihistamines have prominent anticholinergic actions which may contribute to the CNS stimulation seen in some patients. Overdose of various classic H1 antagonists was repeatedly reported to result in toxic psychoses with hallucinations. With "second generation"/piperidine drugs, they do also occur. Directs central nervous system actions of tricyclic antidepressant cause hallucinations. Antimuscarinic effects are especially pronounced with amitriptyline and less with imipramine and clomipramine. Concerning serotonin uptake inhibitors, hallucination can be the result of its anticholinergic properties but also in case of serotonergic syndrome. Monoamine oxidase inhibitors overdose causes hallucinations for the same reason.

The neurochemical changes occurring in PD and DLB strongly support a central role of cholinergic and serotonergic imbalance (cholinergic hypoactivity and serotonergic hyperactivity), both in cortical visual areas and in the brainstem, for the genesis of visual hallucination. In addition, Lauterbach suggested that SRI drugs may induce psychotic symptoms by serotonin receptor (5-HT-3) mediated dopamine release in the ventral striate¹⁶.

Benzodiazepine can produce visual hallucinations. Elderly patients are especially at risk and should take lower-than-usual dose. Baclofen is known in case of abrupt discontinuation to produce withdrawal symptoms including hallucinations. It inhibits GABA-mediated spinal reflexes and is variously postulated to inhibit dopaminergic activity or to enhance it by amphetamine-like effect.

Ketamine is currently used as an antihyperalgesic and opioid-sparing agent during the perioperative period. It can also be used as recreational use.

Hallucinations under antiepileptic are described and also in case of withdrawal¹⁷: valproic, zonisamide¹⁸, carbamazepine¹⁹, levetiracetam²⁰, topiramate and anti-N-Methyl-D-Aspartate receptor encephalitis²¹.

Opioid agonists are marketed as strong analgesics (fentanyl, morphine and methadone), mild-to-moderate analgesics (codeine...), antitussives (codeine, dextrometorphan), antidiarrheals (loperamide), anesthesia adjuncts (fentanyl, sufentanyl)... Their psychomimetic effects include hallucinations. Tramadol has mu-agonist properties and also inhibits reuptake of norepinephrine and serotonin which can explain his higher ROR.

Methylphenidate is a piperidine derivative structurally related to amphetamine. It is marketed for narcolepsy and attention deficit disorder. Hallucination is then a well-known and important identified risk of methylphenidate.

Concerning beta-adrenergic blocker, it is claimed that lipophilic agents, such as propranolol and metoprolol can cross the blood-brain barrier, whereas hydrophilic beta-blockers cannot. The mechanism of metoprolol-induced delirium is not fully understood. It could be due to impairment of hepatic metabolism (especially in the ageing liver) and complex neurotransmitter-related effects on brain beta-adrenoceptors and serotonin (5-HT) receptors²². According Middlemiss, propranolol also possesses serotonin-antagonist properties²³.

Glucocorticosteroids cause a variety of behavioral abnormalities including schizophrenic-type psychosis. Tacrolimus is usually given with corticosteroids and so the specificity of hallucination is difficult to define.

Hanneken hypothesized that proton pump inhibitors (PPI) may disrupt normal horizontal cell-photoreceptor cell feedback interactions and thereby alter spatial and chromatic perception. They demonstrated that PPI with the core structure 2-pyridyl-methylsulfanyl benzimidazole can induce or enhance visual hallucinations in wet macular degeneration patients with a breakdown of the outer blood-retinal barrier²⁴. Another explanation for those hallucinations is the hyponatraemia which can be induced by PPI.

Montelukast is a leukotriene receptor antagonist used in treatment of asthma and has been described to induce hallucination^{25,26}.

Although adverse drug reactions are a well-recognized cause of mental status changes in the elderly, antimicrobials are not often implicated.

Visual hallucinations are rare among patients who are only taking fluoroquinolones but are relatively frequent among patients using multiple medications. Visual and other sensory symptoms are usually dose related and transient. Fluoroquinolones dose regimens should be reduced in cases of renal

failure. In an experimental study, Segev determined that fluoroquinolones displace the Gamma-aminobutyric acid (GABA) from its receptor, resulting in the general stimulation of the central nervous system, which is the basis for this adverse effect^{27,28}. GABA receptor antagonism of fluoroquinolone can maybe explain their neurological properties including the hallucination. Fluoroquinolone should be avoided in patient with psychotic disorder. Only few cases of levofloxacin induced hallucinations have been described in literature²⁹. Our 49 cases allow us to specify the profile of patients.

Other antibiotics can be involved as ertapenem which is a carbapenem antibiotic with a high lipophilicity, a central nervous penetration, and a great volume of distribution. Because both clarithromycin and tramadol are metabolised by CYP3A4 in the liver, symptoms were worsened by the drug-drug interaction³⁰.

Concerning antifungal azoles³¹, systematic therapeutic drug monitoring of voriconazole is mandatory for some authors because of the risk of CYP polymorphism resulting sometimes in hallucination³². Multiple regression analysis of voriconazole concentration according to Dolton and *et al.* found associations between increasing patient age and coadministration of proton pump inhibitors and increased concentrations³³.

When prescribing antimalarial agents³⁴, neuropsychiatric reactions occur even during a prophylactic use of mefloquine and are well-described.

Neurotoxicity secondary to acyclovir is associated with high plasma concentrations. Valaciclovir is the L-valyl ester of acyclovir that is rapidly metabolized to yield acyclovir and valine. Hallucination is especially likely in the presence of renal insufficiency.

Efavirenz, another antiviral used in Human Immunodeficiency Virus has according

Gatch a LSD-like activity mediated via the 5-HT(2A) receptor³⁵.

The mechanisms of drug-induced hallucinations are poorly understood and probably numerous. Anyway 5-HT2A receptors seem to be clearly involved^{36,37}.

We can hypothesize that interaction or renal failure can induce overdose and expose elderly patients to conditions which result in hallucination as hyponatraemia, encephalopathy and serotonin syndrome.

Some limitations of this retrospective study deserve to be mentioned. There are several potential pitfalls inherent to the use of disproportionality measures in spontaneous reporting databases to estimate risk. For example, selection bias due to spontaneous reporting³⁸ (such as underreporting and notoriety bias). However, as stated by Manesse *et al.*³⁹, non-selective underreporting and overreporting does not have any significant influence on the ROR estimation, since it affects both the numerator and the denominator.

The inaccuracy of several observations cannot lead us to exclude other aetiologies as toxicomania when we know for instance that the scores on a hallucination proneness correlated positively to use of cannabis⁴⁰.

The difficulty to distinguish drug effects from those of the underlying disorder is an obvious problem. The temporal relationship and the effect of dechallenge are particularly important in assessing the role of the drug. Anyway, we cannot exclude multifactorial causes, especially in the elderly with poly-medication. In those cases, iatrogenic hallucination secondary to medications seems to be preventable. Compliance with safety precautions is more necessary than ever and those drugs should be also avoided in patient with psychotic disorder.

Conclusions

There is a long list of compounds that may lead to hallucinations, among which zolpidem is the most common. Early diagnosis of drug-induced hallucination and withdrawal of the offending agent is essential. It can be prevented by avoiding polypharmacy and adhering to the saying 'start low and go slow'. Special care is also needed when prescribing for people with renal impairment or in the elderly and for patient with psychotic disorder.

This study has been presented to draw attention of the psychiatrists and other health professionals to the hazardous effect of medications on mental health and especially with non psychiatric medication.

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