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CASE REPORT

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Abusive Prescription of Psychostimulants: A Study of Two Cases

ABSTRACT: Because psychostimulants have serious possible side effects and particular potential for abuse, their therapeutic indications are today exclusively limited to disorders such as obesity, narcolepsy, or attention deficit/hyperactivity disorder. We report two cases of abusive prescription of these drugs. The first concerns a woman who was treated for a 3 kg weight gain with fenproporex for 5 years and presented a withdrawal syndrome when this drug was no longer marketed in France. In the second case, a woman who complained of atypical sleep problems was prescribed modafinil, methylphenidate, clobazam, lormetazepam, meprobamate, and acepromazine, and was found dead in her home a few weeks later in unexplained circumstances. For these two patients, neither the indications, nor the contraindications, nor the prescribing rules for these restricted drugs had been complied with. This case report highlights the extreme danger of these substances and stresses the importance of adhering to the rules of prescription.

KEYWORDS: forensic science, stimulants, fenproporex, modafinil, methylphenidate, prescription

Stimulants include very heterogeneous molecules, the majority being amphetamines and similar substances. Their illicit use has become much more widespread, in particular for leisure purposes or in the attempt to improve performance. However, their therapeutic indications are now largely restricted to disorders such as obesity, narcolepsy, or attention deficit/hyperactivity disorder (ADHD). The rules of prescription and delivery in these indications are extremely strict because of the gravity of the side effects of these molecules, which naturally include the risk of abuse and dependence. We present two cases of abusive prescription of psychostimulants, which clearly illustrate their extremely dangerous nature. The drugs involved were, in the first case, fenproporex, an anorexigenic amphetamine derivative used in the treatment of major obesity, and in the second case, modafinil, a postsynaptic α-1 receptor agonist and "wake-promoting" agent, and methylphenidate, an amphetamine-like psychostimulant, which are used in the treatment of disorders of sleep, alertness, and concentration. From a medicolegal viewpoint, noncompliance with the prescribing rules for these restricted drugs involved the legal responsibility of the prescribing physicians. This type of affair appears to be extremely rare in France, as a study of French case law revealed that there has been only a single conviction to date (1).

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Case Report No. 1

A woman aged 45 years, with no previous history except for a road traffic accident and head injury a few years earlier, presented a depressive syndrome, which she herself considered as minor and which did not affect her professional or private life, accompanied by a weight increase of 3 kg. This weight increase led her to seek the advice of her general practitioner, who prescribed the following treatment for a period of 2 months:

- fenproporex retard 20 mg (Fenproporex retard®, Lab. Theranol Deglaude, Paris, France), one tablet/day,
- fluoxetine 20 mg (Prozac®, Lilly France SAS, Suresnes, France), a serotonin-uptake inhibitor antidepressant, three tablets/day,
- lorazepam 2.5 mg (Temesta®, Biodim, Boulogne-Billancourt, France), a sedative benzodiazepine, one tablet in the evening.

The patient did not lose weight with this treatment, but nevertheless wished to continue it because of her improved mood. She was in the habit of visiting her doctor every month, and was given a monthly prescription for fluoxetine and lorazepam for 2 years and for fenproporex for 5 years. The patient gradually ceased all professional and then social activity and, as she herself stated, was no longer able to carry on her daily activities without taking her fenproporex tablet. She described *a posteriori* the effects of fenproporex as a "cycle" with euphoria followed by aggressive behavior and then despondency. It was never suggested to her during this period that she should attempt withdrawal. When fenproporex was withdrawn from the French market in 1999 for lack of efficacy in the treatment of obesity, the patient presented a major withdrawal syndrome, compulsively seeking the drug, with aggressive behavior, anxiety, irritability, nightmares, and insomnia,

followed by severe depression. Her treating physician again prescribed fluoxetine and lorazepam. Her depression gradually worsened, until she was admitted to a psychiatric unit after a suicide attempt. Several years after discontinuation of the treatment, she still has persistent depression with suicidal ideation, disturbances of attention and concentration, intense asthenia, anhedonia, and headaches.

Case Report No. 2

A woman aged 34 years, with a severe psychiatric history of anorexia, depression, and substance abuse, in particular of amineptine, a dopaminergic antidepressant with a disinhibitory effect indicated in the treatment of endogenous, reactive, or neurotic depression, consulted a general practitioner for insomnia refractory to the usual treatments and daytime sleepiness. The physician diagnosed excessive daytime sleepiness associated with narcolepsy and prescribed the following treatment for a period of 30 days:

- modafinil 100 mg (Modiodal®, Cephalon France, Maisons-Alfort, France), four tablets/day,
- methylphenidate 10 mg (Ritalin®, Novartis Pharma SAS, Rueil Malmaison, France), four tablets/day,
- clobazam 20 mg (Urbanyl®, Sanofi-synthelabo, Paris, France), a sedative benzodiazepine, three tablets/day,
- lormetazepam 2 mg (Noctamide®, Schering SA, Lys-Lez-Lannoy, France), a hypnotic benzodiazepine, four tablets in the evening,
- meprobamate-acepromethazine (Mepronizine®, Sanofi-Synthelabo, Paris, France), a hypnotic associating a carbamate and a phenothiazine, three tablets in the evening.

The treatment was renewed twice. A few weeks later, the patient was admitted to intensive care for probable drug overdose. Emergency tests showed blood benzodiazepine above therapeutic levels (with no further details) and low potassium levels. The psychiatrist called during this episode described the patient as cachectic, extremely agitated, with incoherent speech, complaining of episodes of major anxiety, and worsening of her sleep problems. She discharged herself from hospital against medical opinion and was found dead at her home a few days later. The autopsy carried out after exhumation was unremarkable except for severe cachexia. Toxicological analyses were performed on postmortem gastric content, urine, and hair by immunochemical methods as well as liquid chromatography with diode-array detection (LC/DAD) and gas chromatography with mass spectrometry (GC/MS). These confirmed the presence of meprobamate, acepromethazine, modafinil, clobazam, and lormetazepam. In the absence of a blood sample no quantitative measurement was made. Lastly, it was noteworthy that methylphenidate and its metabolite, ritalinic acid, were not found in any samples, which appears to indicate that the victim had not taken this drug before death. The cause of death could not be established with any certainty.

Discussion

Case 1

Fenproporex diphenylacetate is a phenylethylamine derivative indicated in the treatment of major male-type obesity with a body mass index of 30 or more and after failure of dietary measures (2,3). It was withdrawn from the market in 1999 because of lack of efficacy in long-term management of obesity (4). An initial prescription issued by a hospital specialist in internal medicine, diabetology, endocrinology, and metabolic disorders was mandatory, but this could be renewed by any practitioner on presentation of the original prescription (3). Treatment consisted of courses of 3–6 weeks without exceeding 3 months because of the risk of pulmonary arterial hypertension (3). Finally, the risk of pharmacological tolerance, dependence and withdrawal syndrome after prolonged use was clearly described among the adverse effects of this drug (3). In the present case, it is difficult to give an opinion as to the pertinence of the initial prescription of fenproporex as we have no information on the patient's weight at the time, although she declared she was only slightly overweight. However, it appears evident that the prescribing rules were not complied with, as the patient had had no initial specialized consultation or hospital prescription and the treatment, usually limited to 3 months, was continued for more than 5 years. Moreover, the prescriber took no account of the risk of dependence and withdrawal syndrome, which were nevertheless clearly mentioned among the side effects of this drug. It is noteworthy that in the present case, the risk was probably increased by the fact that at the beginning of treatment lorazepam, an anxiolytic benzodiazepine with a short half-life likely to induce dependence (5), was also prescribed. While fenfluramine abuse is known (6), documented cases of misuse of fenproporex are exceptional. As far as we know, only Nappo (7) has reported fenproporex abuse, in a student population in Brazil, very probably because of more permissive legislation. There is one published case of suicide involving fenproporex (8). While we have little information on the symptoms caused by prolonged use of this substance, there is abundant literature on amphetamines, and we observe that the patient's symptoms corresponded perfectly to those described during the consumption of anorexigenic amphetamines (9). She in fact met three of the DSM-IV criteria for physiological dependence on amphetamines (10): characteristic withdrawal syndrome for the substance, use for longer than the recommended period, and giving up of professional and social activities because of substance use, all occurring within the same 12-month period. Such persons are often also dependent on benzodiazepines (10). However, it is interesting that this patient did not develop tolerance to fenproporex, although this is a classic phenomenon with amphetamine derivatives (10). The explanation perhaps lies in the fact that this was a long-acting form as has been demonstrated for methylphenidate (11). In conclusion, this patient developed genuine dependence on fenproporex induced by abusive prescription. The case illustrates the addictive potential of fenproporex, which although no longer prescribed is freely available on the Internet.

Case 2

Modafinil is a direct agonist of the postsynaptic α-1 receptors. It increases or restores the level of diurnal wakefulness and vigilance but is free from the abuse liability of amphetamines and methylphenidate (12). In France, its prescription was restricted, at the time of this case, to treatment of idiopathic hypersomnia, and narcolepsy with or without cataplexy. Idiopathic hypersomnia and the forms without cataplexy must be documented by nocturnal polysomnography (NPSG) followed by multiple sleep latency testing (MSLT) (13). Modafinil must also be initially prescribed by a hospital department, with annual clinical re-evaluation by a specialist and/or a specialist neurology department or and/or a sleep center (13). Agitation, aggressive behavior and anorexia are cited among the adverse effects. The principal contraindication is major anxiety (13).

Methylphenidate chlorhydrate is a central nervous system stimulant, which is chemically and pharmacologically similar to amphetamines. It is indicated in France since July 1995 (14) for the treatment of ADHD in children aged over 6 years, and since 2000 for the treatment of narcolepsy with or without cataplexy in adults and children aged over 6 years (15). As for modafinil, the forms without cataplexy must be confirmed by NPSG and MSLT (14). An initial hospital prescription made out by a specialist and/or a specialized neurology, psychiatric, pediatric department, or sleep center is mandatory (14,15). In addition, it is on the restricted drugs list and the prescription must therefore be written on a forgery-proof pad and limited to a maximum of 28 days (16). Among its contraindications are major anxiety and psychotic manifestations, and adverse effects include the risk of insomnia, anorexia, and dependence (14). In the case we report, the pertinence of the diagnosis of narcolepsy is particularly difficult to evaluate. The only elements mentioned in the patient's record in this regard were severe insomnia associated with daytime sleepiness, which are inadequate to establish the diagnosis of narcolepsy. Moreover, there is no mention of any episodes of cataplexy, whereas in forms of narcolepsy without cataplexy, it is imperative to confirm the diagnosis by NPSG and MSLT (17), which was not done in this patient. The diagnosis does not therefore seem to be based on any tangible findings. Lastly, according to the psychiatrist who followed the patient during the preceding months, her sleep disturbances were related to indiscriminate consumption of coffee and benzodiazepines. Concerning the prescription *stricto sensu*, multiple faults were committed. It appears first of all that the rule of prescription limited to 28 days (16) was not adhered to, as the first prescription for methylphenidate was for 30 days. Then, as in the preceding case, the patient did not benefit from the initial specialized consultation, which would certainly have been followed by the complementary investigations mentioned above. Moreover, modafinil and methylphenidate were prescribed in association, whereas methylphenidate must only be prescribed after initial treatment modafinil has failed. Lastly, noncompliance with the contraindications and cautions for use was flagrant. The risks of aggravation of anorexia and of rebound anxiety were manifestly not taken into account, but the most remarkable feature of this prescription is undoubtedly the association of several potentially very addictive molecules in a patient with a history of amineptine dependence. Methylphenidate, with high abuse potential (18), was in fact prescribed in association with benzodiazepines and meprobamate, whose abuse potential, although little known, seems perfectly real (19). The responsibility borne by these agents in the aggravation of the psychiatric disturbances and the occurrence of death is another problem. It is probable that the patient did not take the methylphenidate. On the other hand, it is difficult to assess the development of dependence on these substances from the information we have available. However, consumption of modafinil may very likely have increased the patient's anorexia and anxiety without any beneficial effect on the sleep problems. Overall, the two cases confirm that these psychostimulants are highly toxic and that they must be prescribed with great caution.

Legal viewpoint: study of French case law has revealed only a single conviction, for second-degree murder and facilitation of the use of restricted drugs by others, of a practitioner who had prescribed a morphine derivative to a patient who was a drug addict (1). In another case, a practitioner was tried for second-degree murder after issuing a magistral preparation (prescription of a medical product for an individual patient on the basis of a prescription written by a physician and giving detailed instructions on the name of individual components, their amount, and the desired presentation) for amfepramone, an anorexigenic amphetamine derivative whose prescription in this form is prohibited in France, but he was acquitted because the dose prescribed was much lower than the maximum dose recommended by the Dictionnaire Vidal® (20). Legal action has been taken against physicians in relation to drug use in high-level sport, but this is outside the scope of the present paper.

The practitioners involved in the present two cases complied with none of the prescribing rules concerning these restricted drugs, although the rules are clearly set out in the directions for use of these drugs as well as in the Dictionnaire Vidal®, the prescribing manual that is updated every year. The legal responsibility of the two practitioners was naturally implicated; the first was indicted for administration of harmful substances, and the second for second-degree murder by deliberate breach of a particular obligation of safety or prudence and illegal prescription of poisonous substances. Judgment has not yet been rendered in these two cases. The Conseil Régional de l'Ordre des Médecins (regional medical council), the body responsible for disciplinary measures, will give a ruling only when the judge of the criminal court has rendered a verdict, and it must take the judge's observations into consideration but is not bound to follow his conclusions.

Where pharmacists are concerned, one case is recorded of conviction for a breach of the law concerning trade or use of poisonous substances, involving two pharmacists who had dispensed magistral preparations combining two anorexigenic amphetamine derivatives, amfepramone, and fenfluramine (we were unable to trace the conviction of the physician who had prescribed the preparation) (21). In the two cases we present here, as far as we know no legal action was taken against the pharmacists involved, even though they had evidently ignored the absence of an initial hospital prescription, which they should have checked (22). On the other hand, as no methylphenidate was found in the victim's body, we cannot express an opinion as to any violation of the prescribing rules for restricted drugs (16).

In conclusion, these two cases emphasize the dangerous nature of these psychostimulants and also shed particular light on the prescribing rules for restricted drugs in France. While it appears evident that any practitioner must be extremely cautious in prescribing such drugs, nevertheless if prescribing rules are scrupulously adhered to, in particular the initial prescription by a specialist hospital physician, such accidents should be avoided.

References

1. Appeal Court. Criminal chamber. Appeal No 04-82656. [In French]. http://www.legifrance.gouv.fr/WAspad/RechercheExperteCass.jsp
2. Halpern A, Mancini MC. Treatment of obesity: an update on anti-obesity medications. Obes Rev 2003;4:25–42.
3. Dictionnaire vidal. Paris: Editions du Vidal; 1998.
4. Amphetamine anorectic agents: withdrawal of all drug batches. [In French]. Agence Française de Sécurité Sanitaire des Produits de Santé. October 19, 1999.
5. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry 2004;65:7–12.
6. Lawless-Liday C, Force RW. Lessons from the fenfluramines: antiobesity medications are frequently misused. Ann Pharmacother 2000;34:404.
7. Nappo SA. Consumption of anorexigenic amphetamine-like drugs (diethylpropion, fenproporex and mazindol) and of d,1-fenfluramine in Brazil during the years of 1988 and 1989. Pharmacoepidemiol Drug Saf 1996;5:19–25.
8. Bell RR, Crookham SB, Dunn WA, Grates KM, Reiber TM. A contemporaneous finding of fenproporex in a polydrug suicide. J Anal Toxicol 2001;25:652–6.
9. Miller NS, Millman RB, Gold MS. Amphetamines: pharmacology, abuse and addiction. Adv Alcohol Subst Abuse 1989;8:53–69.

10. Crocq MA, Guelfi JD. American Psychiatric Association—DSM-IV-TR. Diagnostic and statistical manual of mental disorders. Revised 4th ed. Paris: Masson; 2003:257–67. [In French].
11. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder: proof-of-concept and proof-of-product studies. Arch Gen Psychiatry 2003;60:204–11.
12. Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacol 2000;14:53–60.
13. Treatment information sheet. [In French] Official Journal of the French Republic (JORF) no 259, November 7, 1999;16638. http://www.legifrance.gouv.fr/WAspad/RechercheSimpleTexte.jsp
14. Marketing Approval no 339 294-0 of July 31 1995, revised September 4 2000, for the specialty RITALINE® 10 mg, tablet. [In French] Holder: Novartis Pharma S.A., 2 et 4, rue Lionel Terray, 92500 Rueil-Malmaison, France.
15. Order of 21 July 2000 modifying the list of pharmaceutical specialties reimbursed to beneficiaries of social security. [In French] Official Journal of the French Republic (JORF) no 177, August 2, 2000;11946. http://www.legifrance.gouv.fr/WAspad/RechercheSimpleTexte.jsp
16. Decree no 99-249 of March 31 1999 relative to poisonous substances and to organization of evaluation of pharmacodependence modifying the code of public health. [In French] Official Journal of the French Republic (JORF) no 77, April 1, 1999;4847. http://www.legifrance.gouv.fr/WAspad/RechercheSimpleTexte.jsp
17. Chakravorty SS, Rye DB. Narcolepsy in the older adult: epidemiology, diagnosis and management. Drugs Aging 2003;20:361–76.
18. Kollins SH, MacDonald EK, Rush CR. Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. Pharmacol Biochem Behav 2001;68:611–27.
19. Bailey DN, Briggs JR. Carisoprodol: an unrecognized drug of abuse. Am J Clin Pathol 2002;117:396–400.
20. Appeal Court. Criminal Chamber. Appeal no 99-85140. http://www.legifrance.gouv.fr/WAspad/RechercheExperteCass.jsp
21. Appeal Court. Criminal Chamber. Appeal no 03-81873. http://www.legifrance.gouv.fr/WAspad/RechercheExperteCass.jsp
22. Decree no 94-1030 of December 2 1994 relative to the conditions of prescription and delivery of medications for human use and modifying the code of public health. [In French] Official Journal of the French Republic (JORF), no 280, December 3, 1994;17080. http://www.legifrance.gouv.fr/WAspad/RechercheSimpleTexte.jsp

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