

# Neonatal Abstinence Syndrome Following Tianeptine Dependence During Pregnancy

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Tianeptine, an atypical antidepressant, has been found to exhibit a potential for abuse. The use of therapeutic doses of tianeptine during pregnancy has never raised safety concerns. However, the impact of tianeptine abuse on the mother-child dyad has never been assessed. We report herein the case of a female patient who presented with dependence on tianeptine, with the use of >650 mg of the drug per day. She had 2 successive pregnancies with similar doses. The state of dependence remained unidentified throughout the first pregnancy, but just after delivery, her full-term newborn exhibited unexpected neonatal abstinence syndrome (NAS). The NAS was successfully treated with morphine, although both the mother's and newborn's urine drug screen was negative. The causality of tianeptine in inducing NAS was retrospectively assessed as "probable" by using a validated causality algorithm. During the second pregnancy, this patient sought addiction treatment and was admitted for residential detoxification treatment in her seventh month of pregnancy. Delivery occurred at full term with a low birth weight neonate. No further developmental insults or medical problems were subsequently identified in the 2 children. Maternal tianeptine dependence during pregnancy may induce a type of NAS that mimics opiate NAS. This finding appears to be consistent with a recent finding of the agonist action of tianeptine on the opiate  $\mu$ -receptor.

Tianeptine is an antidepressant drug approved in several countries within Europe, Latin America, and Asia. The exact molecular mode of action of tianeptine is still not completely understood. Initially, the therapeutic effects of this molecule were attributed to an increase in dopamine and serotonin reuptake.<sup>1</sup> Other studies have found that tianeptine induces modulation of the glutamatergic system.<sup>2</sup> More recently, experimental data suggested that tianeptine also exhibits opiate  $\mu$ -receptor agonist properties.<sup>3</sup>

Previous articles noted that tianeptine use carries a potential for abuse, and can induce a withdrawal syndrome

at supratherapeutic doses.<sup>4,5</sup> The therapeutic use of tianeptine during pregnancy has not raised any safety concerns until now.<sup>6</sup> However, the impact of using tianeptine at supratherapeutic doses during pregnancy has not been previously evaluated. We hereby report the case of 2 successive pregnancies in a context of severe maternal dependence on tianeptine, which led to subsequent neonatal abstinence syndrome in the first neonate. The reported case is described herein according to the CARE Report (CARE) checklist.<sup>7</sup>

## abstract

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All the authors met and treated the patient or her children. All authors provided parts of the medical information described in the manuscript. Drs Bence, Rolland, and Jardri wrote the first draft of the manuscript. All the authors have read and approved the final manuscript.

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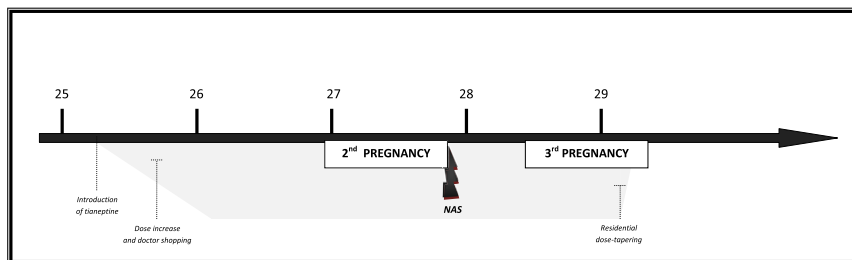
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## CASE REPORT

Ms X is a 29-year-old female patient with no notable history of physical disorders. She developed tobacco dependence at the age of 12, and currently smokes 30 cigarettes per day (20 pack-years). At the age of 23, she gave birth to her first child, a 1860-g boy born by cesarean delivery at 36 weeks of gestation. The cesarean delivery was chosen because of threatened preterm labor with fetal heart rate abnormalities. Two years later, she experienced her first episode of major depressive disorder, for which tianeptine was introduced (see Fig 1). Although the depression symptoms disappeared in the following months, her dose of tianeptine slowly increased, and she began practicing doctor shopping to obtain sufficient doses of tianeptine. By 26 years of age, the dose reached approximately 50 tablets (ie, 625 mg) per day. Ms X retrospectively reported that she had already experienced withdrawal symptoms when she had been unable to obtain sufficient amounts of tianeptine.

At the age of 26, Ms X became pregnant again. She was not taking any medications besides tianeptine at that time. She concealed her state of dependence from the physicians who supervised the pregnancy, and no medical problems were reported throughout the prenatal period. Ms X gave birth without complications to a full-term, 3300-g male infant, and she did not breastfeed the newborn. Twenty-four hours after delivery, the child began to display several concurrent symptoms, including high-pitched crying, excessive sucking, poor feeding, regurgitation, sweating, frequent yawning, and sneezing. The first 2 Finnegan scores<sup>8</sup> were  $\geq 12$ , which led to suspicion of opiate neonatal abstinence syndrome (NAS), although both the mother's and newborn's urinary screen revealed no substance use. As recommended based on the Finnegan scores,<sup>9</sup> morphine syrup



**FIGURE 1**

Summary timeline of events (the age of the patient is indicated in abscise). At the age of 25, Ms X received her first tianeptine treatment of a characterized major episode. Although the depression symptoms disappeared in the following months, her dose of tianeptine slowly increased, and she began practicing doctor shopping. By 26 years of age, the dose reached 50 tablets (625 mg) per day. During the entire second pregnancy, she was severely dependent on tianeptine, which remained unnoticed by the medical team. Shortly after the delivery, the child displayed symptoms of NAS, with 2 consecutive Finnegan<sup>8</sup> scores  $\geq 12$ . Although both the mother's and newborn's urinary screens revealed no substance use, morphine syrup was used to treat the newborn, which quickly reduced his symptoms. During the third pregnancy, the patient spontaneously sought treatment of tianeptine dependence. After careful assessment of the risk-benefit ratio, a team-based decision was made to carry out progressive dose tapering and to stop tianeptine use before the delivery.

was introduced to the newborn and tapered over 5 days, which quickly reduced his symptoms. Thereafter, the child was systematically followed by a maternal and child health service, in accordance with the French recommendations,<sup>10</sup> which were inspired by and are very similar to the American guidelines.<sup>11</sup> No medical problems or developmental abnormalities were reported over the following 2 years. However, the maternal dependence on tianeptine persisted.

At the age of 28, Ms X became pregnant for the third time. After 5 months of pregnancy, she consulted an addiction service with the intent of treating her dependence. At this time, Ms X reported using 56 tablets (ie, 700 mg) of tianeptine per day. She expressed an intense feeling of guilt regarding her medical condition and its possible impact on her child. Thus, she was largely treatment-adherent at that time. A 1-month-long supervised tianeptine dose tapering was proposed in a mother-infant psychiatric unit. The tianeptine dose was tapered by 2 tablets each day. During this process, Ms X reported occasional and moderate withdrawal symptoms (ie, insomnia, anxiety, rhinorrhea, and diarrhea), which were treated with

symptomatic drugs (ie, hydroxyzine, paracetamol, and a physiologic salt solution for airway clearance). A complete ultrasound evaluation was performed at the 34th week of gestation. The fetal growth was judged to be appropriate (2022 g, ie, 28th percentile), and the amniotic liquid volume was normal. The child was a girl born by cesarean delivery at full term. She weighed 2685 g. The mother did not breastfeed the newborn. Although only 6 months have passed since birth, no medical problems or developmental abnormalities have been identified in the infant during the systematic follow-up performed by the mother and child health service.

Ms X provided written consent for this case to be published. The entire case described herein was recorded in the French pharmacovigilance database (#LL1401790/#LL20141790).

## DISCUSSION

This case report consists of the first clinical follow-up and description of a state of severe dependence on tianeptine during 2 successive pregnancies and births. Our main finding was that the birth of Ms X's second child was rapidly complicated

by the occurrence of tianeptine NAS in the newborn. The causality of tianeptine for inducing the NAS was retrospectively assessed with the pediatrician (CA) who cared for the first child. By using the Kramer algorithm,<sup>12</sup> a causality tool for evaluating drug withdrawal,<sup>13</sup> the likelihood of tianeptine being the cause of the NAS was determined to be “probable” (see Table 1).

This type of neonatal complication has not been previously described for tianeptine. Probably for this reason, tianeptine NAS was mistaken for an opiate NAS and was successfully treated with morphine syrup, although the maternal urine screening for addictive drugs was negative. The clinical features of tianeptine NAS and the therapeutic effect of morphine should probably be seen in light of the recently found agonist effect of tianeptine on opiate  $\mu$ -receptors.<sup>3</sup> Similarly, the protracted diarrhea and nasal drip reported by Ms X during her supervised tianeptine withdrawal are also suggestive of some opiatelike withdrawal symptoms induced by tianeptine tapering. Previous experimental and clinical data support this hypothesis (eg, the fact that the  $\mu$ -receptor antagonist naloxone was able to effectively treat tianeptine poisoning<sup>14</sup> and that tianeptine reduces opiate withdrawal effects induced by naloxone in morphine-dependent rats).<sup>15</sup>

Overall, except for NAS, no developmental or gestational effects induced by chronic exposure to high doses of tianeptine were identified in the 2 children at the time of this case report. This result is in line with previous reports of the use of therapeutic doses of tianeptine during pregnancy, which has never been associated with teratogenicity or pejorative fetal outcomes until now.<sup>16</sup> Moreover, the progressive and supervised tianeptine dose tapering in Ms X during her second pregnancy was associated with only slight

**TABLE 1** Assessment of the Causality of Tianeptine in the NAS Occurred in the Newborn by Using the Kramer Algorithm

Algorithm Pathway	Algorithm Responses	Score
Axis 1. Previous general experience with drug	- NAS is not a widely known ADR of high-dose tianeptine  - no reference book mentions NAS as a possible ADR of high-dose tianeptine - the clinical experience accumulated with high-dose tianeptine during pregnancy is insufficient so that NAS could likely have been previously reported	0
Axis 2. Alternative etiologic candidates	- no identified preexisting clinical condition in the mother or the newborn - the occurrence of NAS was not consistent with alternative etiologic candidates, notably because the toxicology screen found no drug of abuse in the mother’s urine - NAS does not occur commonly in newborns, in the absence of etiologic candidates	+2
Axis 3. Timing of events	- the timing of the occurrence of NAS is possible to retrospectively assess - the tianeptine-NAS association is not so unusual as to prevent knowing what timing to expect for an ADR of this type - the timing was consistent with a substance NAS - given the type of ADR, the timing and the context were not only consistent with, but as expected for an ADR to tianeptine	+1
Axis 4. Drug levels and evidence of withdrawal	- NAS is a dose-related manifestation  - no measure of tianeptine was available in serum, urine, or other body fluid - due to the delivery, there is unequivocal evidence that the kinetics of tianeptine in the newborn was consistent with a withdrawal process	+1
Axis 5. Drug reinstatement	- absence of reinstatement of tianeptine in the newborn - administration of morphine syrup with rapid improvement of the NAS	0
Axis 6. Second episode of drug discontinuation	- no other episode of tianeptine discontinuation in the newborn	0
Total Score		+4

The algorithm questions were adapted for drug withdrawal according to the instructions given by Kramer et al.<sup>12</sup> The final “+4” score means that the causality of tianeptine for inducing the NAS is “probable.” ADR, adverse drug reaction.

withdrawal symptoms that required the use of symptomatic medications. We acknowledge that the decision to progressively stop tianeptine use by the patient before delivery was made because of the important psychological distress that resulted from the patient’s dependence. However, in practice, these decisions should be made on a case-by-case basis, after careful assessment of the risk-benefit ratio.

In conclusion, herein, we reported the first case of a tianeptine-related opiatelike NAS in a newborn, after severe tianeptine dependence in the mother during pregnancy. Tianeptine withdrawal has already been reported in adult subjects with tianeptine dependence<sup>4,5</sup> but never

previously in a newborn. The causal role of tianeptine in triggering NAS was assessed and found “probable” by using a validated causality algorithm. Nevertheless, the single-case nature of this report may limit the conclusions that can be drawn, and it should essentially serve as a safety warning for clinicians.<sup>17</sup> Finally, morphine syrup appeared to be efficacious for treating the NAS, which provides additional clinical support for the agonist action of tianeptine on the opiate  $\mu$ -receptor.

**ABBREVIATION**

NAS: neonatal abstinence syndrome

## REFERENCES

1. Fattaccini CM, Bolaños-Jimenez F, Gozlan H, Hamon M. Tianeptine stimulates uptake of 5-hydroxytryptamine in vivo in the rat brain. *Neuropharmacology*. 1990;29(1):1–8
2. McEwen BS, Chattarji S, Diamond DM, et al. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. *Mol Psychiatry*. 2010;15(3):237–249
3. Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a  $\mu$ -opioid receptor agonist. *Transl Psychiatry*. 2014;4:e411
4. Leterme L, Singlan Y-S, Auclair V, Le Boisselier R, Frimas V. Misuse of tianeptine: five cases of abuse [in French]. *Ann Med Interne (Paris)*. 2003;154(spec no 2):S58–S63
5. Rouby F, Pradel V, Frauger E, et al. Assessment of abuse of tianeptine from a reimbursement database using ‘doctor-shopping’ as an indicator. *Fundam Clin Pharmacol*. 2012;26(2):286–294
6. Brayfield A. (Coll.). *Martindale: The Complete Drug Reference*, 38th ed.. London, UK: Pharmaceutical Press; 2014
7. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol*. 2014;67(1):46–51
8. Finnegan LP, Connaughton JF Jr, Kron RE, Emich JP. Neonatal abstinence syndrome: assessment and management. *Addict Dis*. 1975;2(1-2):141–158
9. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*. 2014;134(2). Available at: [www.pediatrics.org/cgi/content/full/134/2/e547](http://www.pediatrics.org/cgi/content/full/134/2/e547)
10. Haute Autorité de Santé . Recommandations pour la Pratique Clinique: Propositions portant sur le dépistage individuel chez l’enfant de 28 jours à 6 ans, destinées aux médecins généralistes, pédiatres, médecins de PMI et médecins scolaires [French Recommendations for Clinical Practice: Propositions about the systematic individual screening of children of 28 days to 6 years of age, intended for general practitioners, pediatricians, mother and child health centers, and school physicians]; 2005. Available at: [www.has-sante.fr/portail/upload/docs/application/pdf/depistages\\_individuels\\_28j-6ans\\_-\\_propositions\\_2006\\_2006\\_12\\_28\\_\\_15\\_55\\_46\\_52.pdf](http://www.has-sante.fr/portail/upload/docs/application/pdf/depistages_individuels_28j-6ans_-_propositions_2006_2006_12_28__15_55_46_52.pdf) Accessed November 6, 2015
11. American Academy of Pediatrics, Committee on Children with Disabilities. Developmental surveillance and screening of infants and young children. *Pediatrics*. 2001;108(1):192–196
12. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA*. 1979;242(7):623–632
13. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf*. 2008;31(1):21–37
14. Ari M, Oktar S, Duru M. Amitriptyline and tianeptine poisoning treated by naloxone. *Hum Exp Toxicol*. 2010;29(9):793–795
15. Chu C-C, Shieh J-P, Shui H-A, et al. Tianeptine reduces morphine antinociceptive tolerance and physical dependence. *Behav Pharmacol*. 2010;21(5-6):523–529
16. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2011
17. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Good pharmacovigilance practices and pharmacoepidemiologic assessment; 2005. Available at: [www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf) Accessed November 6, 2015

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