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Risk Management in Tianeptine Abuse in Turkey: A National Experience

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ÖZET:

Türkiye'de tianeptinin kötüye kullanım risk yönetimi: Ulusal bir tecrübe

Amaç: Major depresif atakların tedavisinde kullanılan tianeptin, herhangi bir ilaç veya alkol bağımlılığı veya kötüye kullanımı öyküsü olanlarda bağımlılık potansiyeli olan ve yapısal olarak trisiklik antidepresanlara benzerlik gösteren, ancak farmakolojik olarak farklı özelliklere sahip bir ilaçtır. Bu çalışmada, Türkiye'de tianeptinin kötüye kullanım potansiyelinden doğan güvenlik problemlerini ve alınan risk yönetimi önlemlerini değerlendirmeyi amaçladık.

Yöntemler: Tianeptinin kötüye kullanımıyla ilgili yan etki bildirimleri ve bu ajanla ilgili alınan risk yönetimi önlemleri, Türkiye İlaç ve Tıbbi Cihaz Kurumu Uygulama Yazılımı, Sağlık Bilgileri Enstitüsü (IMS) değerleri, Uppsala İzleme Merkezi (Vigiflow) ve Türkiye İlaç Takip Sistemi kullanılarak retrospektif olarak değerlendirildi.

Bulgular: 2011 ve 2012 yıllarında tianeptinin kötüye kullanımı sonucu meydana gelen üç ölüm vakası ve Risk Yönetimi Dairesi'ne tianeptinin kötüye kullanımıyla ilgili yan etki bildirimlerinin artması neticesinde tianeptin, Türkiye'de 2012 yılının Ekim ayında kontrole tabi ilaçlar listesine dahil edilmiştir.

Sonuç: Tianeptin, diğer trisiklik antidepresanlara göre bazı avantajlara sahip olmasına rağmen, bağımlılık potansiyeli açısından özellikle herhangi bir ilaç veya alkol bağımlılığı veya kötüye kullanımı öyküsü olan hastalarda dikkatle izlenmelidir.

Anahtar sözcükler: Tianeptin, kötüye kullanım, risk yönetimi

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ABSTRACT:

Risk management in tianeptine abuse in Turkey: a national experience

Objective: Tianeptine is used in the treatment of major depressive episodes and has structural similarities with tricyclic antidepressants although it has different pharmacological properties and has abuse potential among patients with a history of dependence or abuse of any drug or alcohol. In this study, we aimed to evaluate the safety problems and risk management measures for tianeptine in Turkey in relation to its abuse potential.

Methods: Adverse event reports noting tianeptine abuse and the risk management measures for use of this agent have been evaluated through retrospective examination of the databases of the Turkish Medicines and Medical Devices Agency, the Intercontinental Medical Statistics (IMS), the Uppsala Monitoring Centre (Vigiflow) and the Turkish Pharmaceuticals Track and Trace System.

Results: After three individual fatal cases were reported in 2011 and 2012 associated with tianeptine abuse and increased tianeptine abuse reports were received by the risk management department, tianeptine has been included in the controlled substances list in Turkey since October 2012.

Conclusion: Although tianeptine has several advantages compared with tricyclic antidepressants, it should be carefully observed for abuse potential especially in patients with the history of dependence or abuse of any drug or alcohol.

Key words: Tianeptine, drug abuse, risk management

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INTRODUCTION

Tianeptine is a drug which is used in the treatment of major depressive episodes (mild, moderate, or severe) which has structural similarities to tricyclic antidepressants while possessing different pharmacological properties. It is a selective serotonin reuptake enhancer, the opposite of the action of selective serotonin reuptake inhibitors (1). Its efficacy and safety have been shown in some depressive populations with comorbidities such as coronary heart disease, headache, and Parkinson's disease (2-5). Reports on excessive consumption of tianeptine have shown that the cause of misuse and

dependence might be due to its psychostimulant effect leading to the development of tolerance at the outset. In addition, there is a strong mode of feeling, and there are physical withdrawal symptoms if it is not taken again (6). A history of dependence or abuse of any drug or alcohol, have been cited as possible risk factors for the development of dependence on tianeptine (7) when it is used to treat mood and/or personality disorders.

Risk management strategies for medicinal products differ around the world and there are many differences in decision making owing to the variations in health care systems, regulatory requirements and procedures, as well as cultures (8,9). Although, risk management perspectives are independent and unique for each country, pharmacovigilance plans in any territory should enable risk management interventions to be acceptable and worthwhile; thus, sharing information between countries enables risk management plans to be more reliable and effective.

In this study, we have summarized the safety problems and risk management issues associated with the abuse potential of tianeptine in Turkey based on a retrospective evaluation of the Turkish Medicines and Medical Devices Agency (TITCK) database.

METHODS

In Turkey, TITCK carries out regulatory management and control on medicinal products and medical devices for human use. The Risk Management Department of the agency manages and follows up safety risks related to all medicinal products. Adverse drug events reported by healthcare professionals and patients are collected and recorded into a national database and also are shared with the Uppsala Monitoring Centre database. These adverse event reports are evaluated by a consulting commission, which is composed of 13 specialist physicians from different institutions. Safety problems from all over the world published by other health authorities such as the United States Food and Drug Administration (FDA), the European Medicines Agency (EMEA), the Medicines and Healthcare products Regulatory Agency (MHRA), the French National Agency for Medicines and Health Products Safety (ANSM) and Health Canada are scanned and evaluated twice a day. Furthermore, a risk management plan should be submitted to the TITCK by the marketing authorization holders during both the NDA/ANDA submission and post-marketing terms, or when a safety concern is identified regarding a medicinal product at any stage of its life cycle.

In Turkey, only one product containing 12.5 mg tianeptine in tablet form is marketed which has been licensed since 1994 for typical major depressive disorder. After the launch of tianeptine, the "special warning and special precautions for use" section of the Turkish "Summary of the Product Characteristics" (SPC) highlighted a dependence and abuse risk for alcohol and narcotic drugs addicts under the age of 50.

At the beginning of 2011, the marketing authorization holder of this product sent an official letter to the Risk Management Department of the TITCK about the safety concerns and abuse potential of the product. Nonetheless, three individual fatal cases in Turkey involving 35, 51 and 38 year-old men were reported to our Risk Management Department (one by a physician and the other two by the police department) at the end of 2011 and at the beginning of 2012. The tablets were ground, dissolved in cologne or water and injected intravenously. In another case reported by a physician in 2011, a 38 year-old patient with a history of heroin addiction, took tianeptine by intravenous administration which caused vein damage requiring surgical intervention.

After these abuse reports about tianeptine, we scanned our pharmacovigilance database for adverse events reported between 2011-2012, in terms of prevalence and cost, for all antidepressants, as well as the proportion of tianeptine in terms of overall prevalence, cost and retail sales in units, in Turkey between 2007-2012 by using the Intercontinental Medical Statistics (IMS) data base. In addition, we evaluated the sales of tianeptine with or without prescription in each city by using the "Turkish Pharmaceuticals Track and Trace

Table 1: Databases that have been scanned during the study

Database	Origin
Turkish Medicines and Medical Devices Agency application software	Turkey
Institute for Healthcare Informatics (IMS)	USA
The Uppsala Monitoring Centre (Vigiflow)	Sweden
Turkish Pharmaceuticals Track and Trace System	Turkey

Table 2: The ratio of number and cost of tianeptine and total antidepressants in Turkey in 2011 and 2012.

Year	Number of drug boxes sold (Unit)		
	Total	Antidepressants	Tianeptine
2011	1,669,545,426	35,928,550 (2.15%)	242,371 (0.06%)
2012	1,707,694,135	37,3343248 (2.18%)	182,968 (0.05%)
		Cost of drug boxes sold (TL*)	
2011	14,879,777,776	378,588,793 (2.54%)	3,996,717 (1.05%)
2012	14,086,562,346	297,699,665 (2.11%)	2,270,633 (0.76%)

*Turkish Lira

Table 3: The number of adverse drug reports about antidepressants and tianeptine in the total adverse drug reports in Turkey in 2011 and 2012.

Year	Number of adverse drug reports		
	Total	Antidepressants	Tianeptine
2011	1102	29 (2.63%)	2 (0.18%)
2012	1925	35 (1.81%)	3 (0.15%)

System" (TPTTS) which has been in service since 2010. The TPTTS is based on identification of each box of pharmaceutical products for human use in the market by overprinting of an unambiguous matrix code. The databases that have been scanned during the study are listed in Table 1.

RESULTS

The market share of antidepressants in units was 2.15% in 2011 and 2.18% in 2012. The market share of tianeptine in units within the antidepressant segment was 0.06% in 2011 and 0.05% in 2012. The market share of antidepressants in value was 2.54% in 2011 and 2.11% in 2012 whereas the market share of tianeptine in value within antidepressants was 1.05% in 2011 and 0.76% in 2012 (Table 2).

In Turkey, 5900 adverse drug events were reported to the Pharmacovigilance Unit between 2005-2012. Among those, 184 (3.11%) reports were about antidepressants and 5 (0.08%) were about tianeptine. In 2011, the total number of adverse drug reports was 1102; 29 (2.63%) reports were about antidepressants and 2 (0.18%) reports were about tianeptine. In 2012, the total number of adverse drug reports was 1925; 35 (1.81%) reports were about antidepressants and 3 (0.15%) reports were about tianeptine (Table 3).

Although, there was a significant decrease in the total sales in units in Turkey between 2007-2012 (Figure 1), there was a significant increase of sales in units between 2011 and 2012 in Artvin and Rize, the cities that are located in North East Anatolia, close to the border of Georgia (Figure 2A). The population of Turkey is about 75 million and the populations of Artvin and Rize are about 167 thousand (0.22%) and 324 thousand (0.43%), respectively; however the market share in units within Artvin was 0.12% in 2011 and 7.86% in 2012. Similarly, the unit market share in Rize has significantly increased from 0.05%

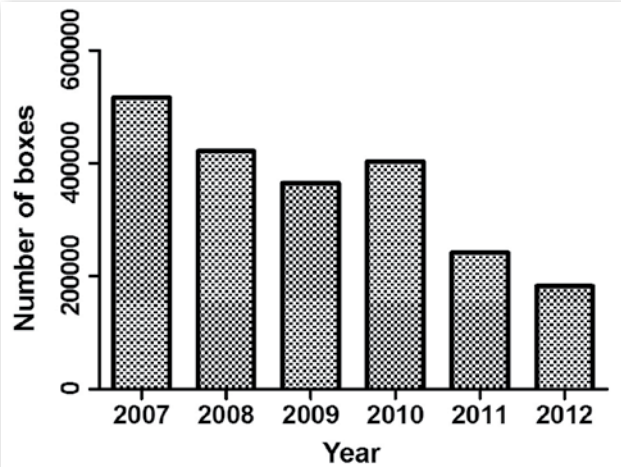

Figure 1: Total number of tianeptine boxes sold from the pharmacies in Turkey between 2007-2012.

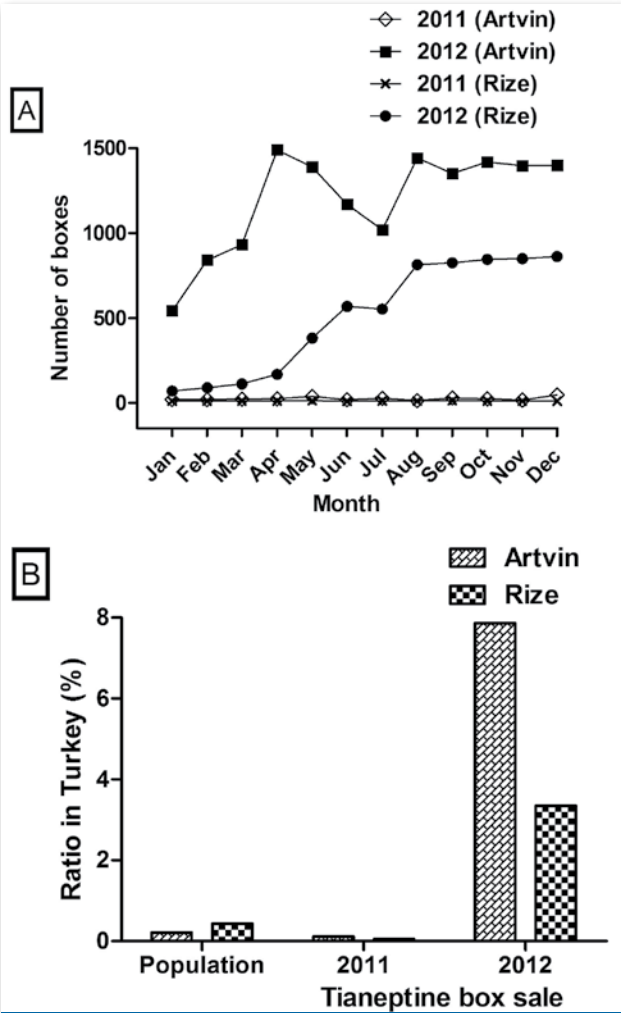

Figure 2: (A) Comparison of number of tianeptine boxes sold from the pharmacies in the Turkish cities of Artvin and Rize in 2011 and 2012. (B) Comparison of the population and the tianeptine boxes sales ratio of the cities of Artvin and Rize with the total in Turkey.

in 2011 to 3.35% in 2012 (Figure 2B).

We have realised that tianeptine has a significant abuse potential; similar reports have been received from health care professionals and the number of reports have increased over time. This subject has been discussed in the Consulting Commission and tianeptine has been included in the controlled substances list that can only be sold with green prescription, a type of prescription used for restricted agents since October 2012. Additionally, tianeptine importation is subject to the "import authorization for controlled substances" and its national consumption and stocks are periodically monitored and controlled by the "Risk Management Department" of the TITCK.

DISCUSSION

Premarketing clinical trials have limited follow-up periods and sample sizes and they also exclude patients with abuse or addiction potential. Thus, evaluation of the abuse potential of a drug is very difficult before its approval (10). Tianeptine has clinical effectiveness in the treatment of major depression, bipolar disorder, and dysthymia or adjustment disorder (11). Clinical trials have shown that tianeptine is well-tolerated, with no significant sedation or increase in body weight, with no significant anticholinergic and cardiovascular effects and that it does not produce changes in hematological, renal or hepatic functions. In addition, it does not cause impairment in cognitive and psychomotor functioning like the majority of the tricyclic antidepressants and it is metabolized by the hepatic cytochrome P450 system leading to fewer drug interactions (2,12).

There have been reports of abuse with antidepressants in the literature but there was no evidence of such risk for tianeptine before its approval in 2005 (13). At that time, tianeptine was thought to have no abuse potential and there was no related information in the SPC before that year. Moreover, several authors recommended its use for patients with preexisting alcohol or drug related disorders (14). After the concerns about the abuse potential of tianeptine arose, researchers focused

on the mechanism of the abuse potential of this agent and they found that it may be mediated by the mesocortico-limbic dopamine pathway, known to be an important part of the psychostimulant effect of drugs. Although the direct effects of tianeptine on dopamine release or re-uptake could be shown (15,16), tianeptine also increased a dopamine metabolite (3,4-dihydroxiphenilacetic acid) in the cerebral cortex and other regions of the brain (16,17). Additionally, Rouby et al. (18) confirmed the specificity concerning the abuse liability of tianeptine compared with other antidepressants. In light of these laboratory data, published case reports and data coming from spontaneous reporting, the French medicine agency took measures concerning tianeptine. Its SPC was modified in 2005, warning against the possibility of addiction especially for subjects with past or current drug or alcohol related disorders (18).

The Georgia Health Authority has withdrawn tianeptine from the market in June 2010 because of its abuse potential. In July 2010, the Health Authorities of Russia and Armenia have included tianeptine in the controlled substances list due to its misuse by drug addicts (intravenous injection). Similar measures have been implemented in the Ukraine in January 2011.

Tianeptine has abuse potential especially in former opiate abusers. The National Narcotics and Psychotropic Agents Commission of the French Health Products Safety Agency (ANSM) have reported, after their meeting in June of 2011, that sales of tianeptine have decreased between 2006 and 2009 but 45 cases of abuse were reported over the same period. The subjects who consumed excessive amount of tianeptine were mainly younger than 50 years old and 61.4% were women. Among the 45 cases reported, 30 subjects had a history of abuse of other agents. Tianeptine dependence and abuse risk was estimated to occur in 1 case out of every 1000 patients treated. The profile of the subjects abusing the drug remained stable over time as women under the age of 50, with a history of drug dependence or abuse, high consumption of daily doses and difficult withdrawal or attempts at withdrawal. They concluded that the risk-benefit ratio of tianeptine remained positive provided actions such as reinforcing and increasing the security of the prescription and dispensing conditions of tianeptine were implemented to minimize the risk of drug dependence and abuse (19).

Three case reports from Turkey concerning abuse of tianeptine have been published between 2006-2011 (7,20-22). After three fatal individual cases in 2011 and 2012 with tianeptine abuse and increased tianeptine abuse reports to our risk management department, tianeptine has been included in the controlled substances list that can only be sold by a green prescription, which is a kind of prescription used for restricted agents since October 2012. Additionally, tianeptine importation requires "import authorization for controlled substances" and its national consumption and stocks are periodically followed and controlled by the Risk Management Department.

In conclusion, although tianeptine has several advantages compared with tricyclic antidepressants, its use should be carefully observed for abuse potential especially in patients with a history of dependence or abuse of any drug or alcohol. Besides, if tianeptine pills could be manufactured in a different, abuse resistant method, it may still provide a good alternative in the treatment of depression and anxiety.

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