Tramadol Abuse and Sexual Function

Ibrahim A. Abdel-Hamid, MD,[1] Karl-Erik Andersson, MD, PhD,[2] Marcel D. Waldinger, MD, PhD,[3] and Tarek H. Anis, MD[4]

ABSTRACT

Introduction: Tramadol exhibits an effect profile similar to that of opioid agonists, and tramadol abuse seems to be a problem for a number of countries. The relationship between tramadol and sexual function appears to be controversial. Men with premature ejaculation (PE) may benefit from taking tramadol off label; however, these patients live "on a knife's edge" and are exquisitely sensitive to develop other sexual dysfunctions.

Aim: To review the literature regarding the problem of tramadol abuse and its relationship with sexual function.

Methods: We searched electronic databases from 1977 to September 2015, including PubMed MEDLINE, EMBASE, EBCSO Academic Search Complete, Cochrane Systematic Reviews Database, and GoogleScholar using the following key words: tramadol, sexual functions, and sexual dysfunction.

Main Outcome Measure: To define the supposed benefits and the potential risks of tramadol on different sexual functions including ejaculation, orgasm, erection, desire, and testosterone levels.

Results: Although tramadol is thought to have low abuse and dependence potentials worldwide, its abuse has become a serious problem in many countries, particularly in the Middle East, Africa, and West Asia. The benefit of tramadol in PE was reported in 11 clinical trials, evaluated by 6 systematic reviews, 3 of which pooled data in a meta-analysis. The evidence base on erectile dysfunction, decreased libido, hypogonadism, anorgasmia, and risky sexual behaviors in patients abusing tramadol is inadequate.

Conclusions: Tramadol may offer a useful intervention for treating PE. As all primary studies had suffered from selection, allocation, performance, or assessment bias, additional rigorous well-designed controlled trials are warranted to further investigate the potential long-term risks of tramadol and to determine the safe and the effective minimum daily dose. Clinical research on drug abuse and sexual dysfunction is an emerging field. To date, small numbers of studies have been performed and further studies are warranted.

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Key Words: Tramadol; Sexual Function; Ejaculation; Erection; Hypogonadism

INTRODUCTION

Tramadol is a prescription atypical synthetic opioid analgesic. The drug activates μ-opioid and monoamine receptor systems. Tramadol has been marketed in Germany since 1977, and in the United States and Sweden since 1995. It has an important wide range of applications in both acute (eg, postoperative, trauma) and chronic (cancer and noncancer) pain, but also may have reinforcing/rewarding effects.[1,2] Tramadol is thought to have limited abuse potential compared with other μ-opioid receptor agonists, but laboratory data have indicated that it shares some of their pharmacodynamic effects.[3] Acute doses of tramadol exhibit a profile of effects similar to those of opioid receptor agonists and may have abuse liability in certain populations.[1] There is evidence that the incidence rate for abuse of tramadol is 69/1,000 persons per year and the dependence rate is 6.9/1,000 persons per year.[4] In the recent International Narcotics Control Board survey,[5] tramadol abuse seems to be a problem for a limited but significant number of countries (32 of the 77 countries responding on that issue).

The relationship between tramadol and sexual function appears to be controversial. Although there is evidence that men with premature ejaculation (PE) may benefit from using tramadol off label,[6,7] these patients are living "on a knife's edge" and are exquisitely sensitive to develop other sexual dysfunctions such

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[1]Division of Andrology, Mansoura Faculty of Medicine, Mansoura, Egypt;

[2]Wake Forest Institute for Regenerative Medicine, Wake Forest University, Winston Salem, NC, USA;

[3]Department of Pharmacology and Physiology, Drexler University School of Medicine, Philadelphia, PA, USA;

[4]Department of Andrology, Kasr Al-Eini School of Medicine, Cairo University, Cairo, Egypt

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as erectile dysfunction or desire disorder,[8,9] secondary hypogonadism,[9–15] decreased sexual self-esteem and overall sexual relationship satisfaction,[16] risky sexual behaviors,[17–19] and drug tolerance[8] and dependency.[12,20–23] The current review seeks to address the problem of tramadol abuse and its relationship with sexual function including PE.

TERMINOLOGY

According to 2 recent consensus statements[24,25] and the associated commentaries of Butler[26] and Sullivan,[27] Vowles et al[28] proposed the following definitions for risky use of analgesics:

A. Misuse: Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects.
B. Abuse: Intentional use of the opioid for a nonmedical purpose, such as euphoria or altering one's state of consciousness.
C. Addiction: Pattern of continued use with experience of, or demonstrated potential for, harm (eg, "impaired control over drug use, compulsive use, continued use despite harm, and craving").

PHARMACOEPIDEMIOLOGY OF TRAMADOL ABUSE

According to Intercontinental Marketing Services (IMS) Kilochem data, the worldwide consumption of tramadol has increased from 290 tons in 2006 to 424 tons in 2012 (42% increase).[29] The International Narcotics Control Board (INCB) incorporated in its annual report for 2013 information on global developments in the nonmedical use and abuse, illicit manufacture, and illicit domestic and international distribution of tramadol. This report[5] demonstrated that 33 countries, approximately 42% of those responding reported nonmedical use and/or abuse of tramadol, mostly providing anecdotal information, and abuse of tramadol (two-thirds of which is oral dosage form abuse) was increasing in 12 of the countries (38%) reporting such abuse and was stable in an additional 13 countries (42%). In addition, 5 countries reported that abuse of tramadol was a significant risk, while illicit trafficking was recorded in a limited number of countries.

Tramadol abuse was stated to have become a serious problem in Egypt, Iran, Jordan, Lebanon, Libya, Mauritius, Saudi Arabia, Togo, and Gaza. Epidemiological reports and surveillance studies indicated that its consumption, abuse liability, dependency, overdoses, and diversion have increased, leading several countries to put tramadol under national control.[2,30–37] These countries include both developed and developing countries such as Bahrain, Mauritius, Iran, Venezuela, Sweden, Ukraine, Egypt, Nigeria, Australia, Brazil, Japan, Lithuania, China, Jordan, Saudi Arabia, the United Kingdom, and the United States. Tramadol was said to have low-abuse and dependence potentials worldwide relative to morphine[35,37–39] that have been confirmed in both preclinical[40,41] and clinical observations.[2,21,34,42–45]

RELEVANT PHARMACOLOGY OF TRAMADOL

Pharmacokinetics

Tramadol is marketed as a hydrochloride salt and is primarily administered orally, although other formulations are available in sublingual, intranasal, intravenous, subcutaneous, and intramuscular administration forms and as rectal suppositories. It also is available in combination with acetaminophen and in immediate-release and extended-release formulations. It is rapidly and almost completely absorbed after oral administration but its absolute bioavailability is only 66%–77% due to first-pass metabolism and increases to almost 100% after multiple doses or after an intramuscular administration.[46–50] In rats, the relative bioavailabilities of the nasal- and buccal-administration forms compared with the oral route are 504.8% and 183.4%, respectively (ie, much higher than that of oral administration).[51]

The recommended daily dose of immediate-release tramadol is 50–100 mg every 4–6 hours. The maximum dose recommended by the manufacturer is 400 mg in a 24-hour period secondary to the increased risk of side effects with higher doses[52]; however, there have been limited clinical reports of its use up to 600 mg/day in carefully selected patients. Tramadol's pharmacokinetic profile is not affected by the intake of food,[53] but after single-dose administration of 200 mg tramadol extended release (ER) with a high-fat meal, the drug's area under the curve (AUC) and maximum concentration (C_{max}) decreased by 16% and 28%, respectively. In addition, its half-life is extended to 17 hours, compared with 14 hours in fasting conditions.[54] Peak plasma tramadol levels after oral, rectal, and intramuscular intake are reached in 1–2 hours, 3 hours, and 45 minutes, respectively. The drug has a terminal half-life ($t_{1/2}$) of about 5–6 hours.[49,55] This relatively short half-life results in a required dosage frequency of 4–6 times daily.[55,56] Extended-release preparations provide smoother plasma concentration profile, a longer half-life (10–13.4 hours) and have lower (about half) peak concentrations after 4 to 6 hours.[56] Plasma protein binding is ~20% and is rapidly distributed in the body with distribution volume (V_d) of 2–3 L/kg.[57] Tramadol is extensively metabolized in the liver by demethylation, oxidation, and conjugation (sulfation and glucuronidation).[58,59] Twenty-six metabolites have been recognized (14 phase 1 metabolites and 12 conjugates).[60]

The *O*-desmethylation of tramadol to its main active metabolite, *O*-desmethyltramadol (M1), is catalyzed by cytochrome P450 (CYP) 2D6.[58] On the other hand, the *N*-desmethylation to *N* desmethyltramadol (M2) is catalyzed by *CYP2B6* and *CYP3A4*.[60] Among all its metabolites, only M1 and, to a lesser extent, *N,O*-didesmethyltramadol (M5), are pharmacologically active.[59,60] Generally, tramadol metabolism is stereoselective (a stereoselective reaction is one in which the pathway allows formation of both products, but 1 product is preferred over the