Tramadol Abuse and Sexual Function

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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.

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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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

other). Phase I *O*-demethylation has been demonstrated to favor (−)-tramadol, while *N*-demethylation favors (+)-tramadol.[61] In addition, *O*-desmethyl-tramadol and *N,O*-didesmethyl-tramadol are the only known active metabolites in tramadol phase II glucuronidation.[62] *CYP2D6* is encoded by a highly polymorphic gene. There are variations of *CYP2D6* allele distribution in populations of different ethnic and geographic origins.[63,64] An estimated 5% to 10% of the Caucasian population possess allelic variants of the *CYP2D6* gene that are associated with reduced clearance of tramadol (poor metabolizers [PMs]) and between 1% to 7% of Caucasian people carry *CYP2D6* allelic variants associated with rapid metabolism (ultrarapid metabolizers [UMs]).[65] Patients who are PMs experience reduced efficacy with tramadol because they have a limited ability to metabolize tramadol into the active molecule, (+)-M1.[66] Conversely, patients exhibiting the UM phenotype are prone to tramadol's opioid-like effects because their rapid metabolism generates a higher concentration of (+)-M1. Accordingly, people from Middle Eastern countries, where tramadol abuse is common, are more likely to be *CYP2D6* UMs, expected to be susceptible to opioid effects such as dependency.[67,68] However, other studies have not been able to show an association between the *CYP2D6* genotype and the clinical response.[69,70] Tramadol is primarily eliminated renally (90%), with the remainder being excreted in the stools.[71] Tramadol is apparently excreted in the following percentages in 72-hour urine: 29% unchanged, 20% *O*-desmethyl-tramadol and its conjugates, 20% *N,O*-didesmethyl-tramadol and its conjugates, 17% *N*-desmethyl-tramadol, with the remainder being other metabolites.[49] These pharmacokinetic properties require dose adjustment in patients with hepatic or renal impairments.

Pharmacodynamics

Pharmaceutical formulations of tramadol consist of a racemic mixture of (+)-tramadol and (−)-tramadol. The exact mechanism(s) of action of the drug remain unclear to a large extent. However, the past decade has witnessed a number of remarkable advances that may clear the pharmacologic actions of tramadol. Overall, the antinociceptive effects of tramadol include both nonopioid components, that is, noradrenergic and serotonergic components, and opioid components acting mainly on the central nervous system (CNS).[72] Other actions include influences on other several G protein−coupled receptors (GPCRs), transporters, and ion channels.[73]

Preclinical and clinical studies showed that the parent drug [(±)-tramadol, the two isomers] is only a weak μ-opioid receptor (encoded by gene *OPRM1*) agonist (4,000-fold less than that of morphine), whereas the metabolite M1 is primarily responsible for tramadol's μ-opioid activity and is significantly more potent than tramadol μ-opioid receptor binding (400-fold higher affinity for the μ-opioid receptor than that of tramadol, one-tenth that of morphine for the μ-opioid receptor)[74−76] and in producing analgesia (one-tenth as potent as morphine when each is administered parenterally, and approximately one-third as potent when each is administered orally).[40] Tramadol metabolites M2, M3, and M4 have negligible affinity for the human μ-opioid receptor.[63−65] Studies of acute dosing show minimal opioid-like effects, yet chronic dosing results in opioid physical dependence and withdrawal on discontinuation.[37,77] The level of physical dependence is related to the dose of tramadol administered. Higher doses of tramadol produce a signal of abuse potential, with increases on some prototypic measures such as "drug liking."[1,2] An accumulation of M1 likely leads to CNS adaptations that are typical of other μ-opioid receptor agonists.[1,2,78] The μ-opioid receptor affinity alone is not sufficient to account for the analgesic action of tramadol. In addition to its action on μ-opioid receptors, tramadol acts on serotonergic and noradrenergic systems thought to be involved in the analgesic effect. Tramadol inhibits reuptake of serotonin, with (+)-tramadol about 4 times more potent than (−)-tramadol, whereas M1 is about 10 times less potent than (−)-tramadol.[79,80] Likewise, acute and chronic administration of tramadol holds the potential to block noradrenaline reuptake with (−)-tramadol being approximately 10 times more potent than (+)-tramadol in rat hypothalamic synaptosomes.[81,82] Other actions of tramadol include experimental evidence of inhibition of 5-nicotinic acetylcholine receptor,[83] 5-hydroxytryptamine (5-HT) type 2C receptor,[84] M1/M3 muscarinic receptor,[85,86] $GABA_A$ receptor,[87] *N*-methyl-D-aspartate (NMDA) receptor,[87] and transient receptor potential ankyrin 1 channel (TRPA1).[88] In addition, there is evidence of involvement of nitric oxide (NO)−cyclic guanosine monophosphate pathway and ATP-sensitive K^+ channels in antinociception by tramadol in the mouse formalin model[89] and the drug may activate the transient receptor potential vanilloid 1 channel (TRPV1).[90] We do not yet know the significance of these later findings on the tramadol abuse; however, most of these receptors are involved in the regulation of sexual function. It also is not known if these actions can be translated from animals into humans.

SEXUAL BENEFITS OF TRAMADOL

Tramadol is prescribed off-label for the treatment of PE, a common male sexual complaint.

Rationale

The mechanism(s) by which tramadol delays ejaculation is (are) still not clearly identified. Several physiological and pharmacological observations have been hypothesized to explain the effects of tramadol in delaying ejaculation: (a) systemic administration of morphine exerts inhibitory effects on ejaculatory behavior[91] and reflexes in male rats[91−93] partially mediated via actions on peripheral tissues,[93] suggesting a role for opioid receptors in the regulation of ejaculation. However, there is evidence that lower dosages of opioid receptor agonists have facilitative effects whereas higher dosages have inhibitory effects on the ejaculatory reflexes.[94] These variable effects of opioid receptor agonists may be due to differences in the site of actions

(central or peripheral; presynaptic or postsynaptic) or desensitization of the receptors at the target sites. In general, μ and $\delta-$ opioid receptors are inhibitory G protein—coupled receptors[95]; therefore, it is possible that endogenous opioids trigger or facilitate ejaculatory reflexes by means of inhibition of inhibitory neurons in lumbar spinothalamic neurons target regions.[94] It is obvious that the effects of opioid agonists are complicated. (b) Tramadol inhibits reuptake of serotonin[79,80] and animal studies as well as clinical investigations have shown that serotonin plays a central role in the control of the ejaculatory threshold.[96,97] Drugs inhibiting serotonin reuptake demonstrated prolongation of intravaginal ejaculation latency time (IELT) and showed efficacy in the treatment of PE.[97] (c) Tramadol inhibits noradrenaline reuptake.[81,82] The effects of noradrenaline on ejaculation are dose-dependent, with low doses facilitating and high doses inhibiting ejaculation in male rats.[98] (d) Tramadol has an inhibitory effect on NMDA receptors[87] that has been demonstrated to facilitate ejaculation through lumbosacral spinal mechanisms.[99] (e) Tramadol has an inhibitory effect on M1 and M3 muscarinic acetylcholine receptors[85,86] that are the relatively dominant subtypes on rat seminal vesicles,[100] whereas the sympathetic effect is dominant during emission to squeeze seminal fluid out, the parasympathetic effect is dominant during ejection to provide an antireflux effect on the ejaculatory duct, suggesting a role of parasympatholytic actions in modulation of ejaculation. In addition, there is experimental evidence that the muscarinic receptor agonist shortens the ejaculatory latency in a dose-dependent way.[101] (f) Tramadol is known to exhibit anesthetic-like effects in the peripheral nervous system[102,103] through inhibition of spinal somatosensory evoked potentials, with the fast conducting fibers more susceptible to tramadol than medium and moderate fibers, and tramadol possibly acts on the Na^+ and K^+ channels activity rather than passive properties (such as space and time constant) of nerve fibers.[102,103] Additionally, it has been shown that preparations with local anesthetic effects are beneficial in the treatment of PE through reduction of penile hyperexcitability and prolongation of sensory conduction.[104]

Findings

The evidence for the benefit of tramadol in PE was reported in 11 clinical trials,[8,105–114] 10 trials,[8,105–113] evaluated by 6 systematic reviews,[6,7,115–118] 3 of which pooled data in a meta-analysis,[6,7,118] and 1 further randomized clinical trial (RCT).[114] However, the search methodology and inclusion criteria varied across these reviews. Using Assessment of Multiple Systematic reviews (AMSTAR), the overall AMSTAR quality score was 1/11 in 2 of the reviews,[115,117] 2/11 in another review,[118] 6/11 in the last,[6] 10/11 in 1[7] and 11/11 in the last.[116] Treatment duration was 3 to 24 weeks.The long-term side effects, including addiction or abuse potential, for men with PE have not been evaluated. Most of the studies pooled were clinically and statistically heterogeneous; the majority were of unclear methodological quality due to limited reporting. A high level of statistical heterogeneity is evident ($I^2 = 74\%$).[6,7,118] Most of the primary studies pooled in the meta-analyses suffered from selection, allocation, performance, or assessment bias.[6,7,118] Pooled evidence demonstrated the therapeutic advantage of tramadol over placebo in the treatment of PE at increasing IELT over 8 to 12 weeks and improved sexual satisfaction. Another problem has been raised in the latest meta-analysis study,[7,119] the largest between-group effect size (3.52 minutes) was notable for 1 RCT.[105] The authors of the meta-analysis study[7] raised concern over this primary study[105] because 3 clinical studies by the same investigator were retracted in the past 3 years. However, excluding this RCT from the analysis did not significantly alter the overall effect size (1.02 minutes) or reduce the between-trial heterogeneity ($I^2 = 71\%$). The variability across RCTs in terms of drug dosage and treatment duration did not permit identification of a safe and effective minimum daily dose.[6,7,118] The results from 1 RCT showed that tramadol combined with behavioral therapy was significantly more effective than behavioral therapy alone.[108] The evidence from 1 RCT indicated that there is no difference in IELT between tramadol taken 2 to 3 hours before planned intercourse and paroxetine daily.[107] In contrast, another RCT demonstrated that as-needed tramadol is better for prolonging the IELT (nearly twice as good) than on-demand paroxetine 4 hours prior to the planned intercourse.[109] Both of these trials suffered from allocation and assessment bias. Pooled evidence across trials [7,105,107,110–112] showed that tramadol is associated with significantly more adverse effects including erectile dysfunction, constipation, nausea, headache, somnolence, dry mouth, dizziness, fatigue, pruritus, and vomiting, than placebo or behavioral therapy over 8 to 12 weeks of treatment.

Conclusions

Tramadol may offer a useful intervention for treating PE. As all of the primary studies had suffered from selection, allocation, performance, or assessment bias, additional rigorous well-designed controlled trials are warranted to further investigate the potential risks of tramadol in the long-term and to determine a safe and effective minimum daily dose. At this time it may be considered only when other therapies have failed because of the risk of addiction and side effects. Prescribing physicians should be aware of and educate their patients on the potential development of serotonin syndrome (a mild to potentially life-threatening syndrome) associated with tramadol use,[119] selective serotonin reuptake inhibitor interactions,[120] and overdose.[121]

SEXUAL RISKS OF TRAMADOL

Erectile Dysfunction

Rationale

Opiates such as morphine, heroin, and methadone, agonists of the opioid receptors, inhibit copulatory behavior when given

either acutely or chronically in male rats, mice, hamsters, and monkeys.[122–124] Similar results have been noted after the central administration opioid peptides, such as β-endorphin, endomorphin, or *met*-enkephalin analogues.[124–126] These inhibitory effects of opiates and opioid peptides are possibly mediated by opioid receptors because they are prevented by selective and nonselective opioid receptor antagonists.[124,125] The inhibitory role of opioid peptides seems to occur in men.[125] The effect on the penile erection may involve NO[127] and the peripheral opioid receptors that are responsible for at least some of the inhibitory actions of morphine on male sexual behavior.[93] Moreover, ablation of the gene encoding μ-opioid receptors lengthens the period before sexual activity and reduces the sexual activity in homozygous male mice.[128] Furthermore, ED is one of the most common opiate withdrawal signs in male addicts.[129,130] Additionally, the effects of tramadol appear appears to be contradictory. Although there is evidence that tramadol increases dopamine release (which has facilitative effects on penile erection),[131] it inhibits reuptake of noradrenaline and serotonin,[80,81] which have inhibitory effects on penile erection.[132]

Findings

The results of a recent systematic review[133] of long-term opioid therapy for chronic pain clinical trials concluded that compared with nonuse, long-term opioid use was associated with increased use of medications for ED or testosterone replacement (adjusted OR, 1.45, 95% CI, 1.12–1.87).[134] The authors of the primary investigation studied the use of medications for ED or testosterone replacement as proxies for sexual dysfunction among men receiving opioid or nonopioid therapy for pain. Lower doses of opioids were not associated with a higher odds ratio. Thus, the combination of long-term and high-dose opioid use seems to be strongly associated with markers of sexual dysfunction. In the same systematic review,[133] sexual dysfunction was not measured directly in most of the primary studies. Most placebo-controlled, randomized trials were shorter than 6 weeks, and almost all were shorter than 16 weeks. In agreement with these results, Ferrer et al[135] noted that ED is a problem in 90 chronic noncancer pain patients, 41% of whom received tramadol.

In a study done in Egypt, where tramadol abuse is prevalent, El-Hadidy and El-Gilany[16] evaluated 112 tramadol-dependent married men 6 months after treatment from dependency using the Arabic version of the Self-Esteem and Relationship (SEAR) questionnaire for Egypt.[136] They noted that the subscales of sexual relationship, sexual self-esteem, and overall sexual satisfaction showed significant increase post-treatment compared with pretreatment. Another study from India showed that ED was recorded in 45% by IIEF in men seeking treatment for opioid dependence.[22] In addition, ED was the second domain to be affected as measured by the Arizona Sexual Experience Questionnaire and Changes in Sexual Functioning Questionnaire Short-Form. Unfortunately, in this study, only 1% of patients were abusing tramadol, indicating that these results cannot be generalizable to tramadol abusers. ED occurred in 3.33% of patients treated with tramadol.[113] Moreover, Alghobary et al[8] observed that all cases of PE including ISSM-defined group showed significant less erection measured by Arabic Index of Premature Ejaculation score after 6 weeks and 12 weeks compared with the baseline level. In contrast, Wong et al[11] noted that the incidence ED among 26 opioid users and 6 controls was equally present in opioid users and nonopioid analgesic users. Men with ED had lower free testosterone levels regardless of whether they were on opioids.

Conclusions

The evidence base on ED in patients abusing tramadol is limited being based on efficacy and safety trials that lacked direct comprehensive evaluation of ED, or the duration to detect long-term problems such as ED. Most of the quoted studies lacked the statistical power to detect uncommon problems and some did not use a standardized instrument such as IIEF for assessment of ED. Further studies are warranted.

Hypogonadism

Rationale

It is widely recognized that both endogenous and exogenous opioids may induce hypogonadism through binding to opioid receptors in the hypothalamus and pituitary gland. This will lead to decreased release of gonadotropin-releasing hormone or modification of its pulsatility, resulting in decreased release of luteinizing hormone and follicle-stimulating hormone from the pituitary, and consequently decreased gonadal steroid production.[137–139] The other proposed mechanisms may include increased prolactin or decreased dehydroepiandrosterone, which is an important precursor of testosterone.[139,140] These side effects are more commonly linked with exogenous than endogenous opioids, with use of long-acting rather than short-acting opioids, supraphysiologic doses, or drug abuse.[140,141] A late systematic review and meta-analysis[142] pointed out that testosterone is suppressed by almost 50% in some men and is far below the average clinical reference ranges. The authors did not observe the same effect in women, suggesting that men and women have different mechanisms of hormonal disturbance caused by opioids. It is possible that not all opioids produce equal effects on the hypothalamic–pituitary-gonadal axis, which may be of clinical significance. Animal studies in male rats showed no difference among the opioids morphine, fentanyl, tramadol, and buprenorphine on plasma testosterone levels at 4 hours after a single injection,[12] whereas brain testosterone levels are significantly decreased after morphine, fentanyl, or tramadol injection, but not after buprenorphine.[12] Additionally, ample evidence attests to the potential of tramadol to cause testicular toxicity. Chronic administration of tramadol in animals showed histological abnormalities in both brain and testicular tissues possibly induced by oxidative stress in these organs.[13,14,143–145]

Moreover, tramadol may increase the testicular levels of nitric oxide and lipid peroxidation and decrease the antioxidant enzyme activities in male rats.[14] Furthermore; tramadol induces not only a hormonal pattern of hypogonadotropic hypogonadism[13,15] but also decreases the fertility potential of rats and mice testes.[15,146] However, these negative effects of tramadol on testes are dose dependent and are reversible.[147]

Findings

One systematic review[148] demonstrated that testosterone levels are suppressed in men receiving opioids, regardless of opioid type or indication of use. However the authors concluded that there is a lack of high-quality studies to associate chronic opioid pain management with hypogonadism. At present, there is fair evidence to associate hypogonadism with chronic opioid pain management, and only limited evidence for treatment of opioid-induced sex hormone deficiency. There is a large-scale population-based study examining the extent to which opioid use may contribute to changes in testosterone levels.[149] This study included 62 patients receiving tramadol. Participants on opioids had higher odds of having low testosterone levels than those unexposed (OR 1.40, 95% CI 1.07−1.84). However, increasing age and the presence of comorbidities are important risk factors that are also associated with low levels of testosterone. In this study the daily dosage of opioids taken by the participants was not known, so the effect of opioid dose was not assessed. It appears that opioids whose mechanism of action involves inhibition of norepinephrine reuptake may have a lower impact on testosterone levels than opioids whose analgesic effect is only through activation of opioid receptors.[150] In some studies tramadol-treated patients were excluded either due to inability to accurately calculate morphine-standardized equivalent dose or because tramadol was used for reasons other than chronic pain, such as chemical dependency.[138,139] However, there are sporadic case reports that associate hypogonadism in men and combinations of opioids, including tramadol.[10,151] Finally, it has been demonstrated that the frequency of sexual dysfunction did not correlate with hormone levels[11] These data could be explained by the presence of chronic pain that mask the symptoms of hypogonadism.

Conclusions

Examination of the effect of tramadol on gonadal functions in humans has yet to be completed and studies that include samples of men are generally small in this particular area of research. It is still unclear whether tramadol-induced hypogonadism is associated with symptoms. It appears that tramadol-induced hypogonadism is underrecognized in patients with tramadol abuse or addiction. The contribution of the nonopioid component might mitigate against some opioid-induced adverse effects. Sufficient clinical or preclinical investigations on this particular point are lacking.

Anorgasmia

Rationale

The possibility that tramadol could inhibit orgasm comes from the following observations: (a) selective serotonin reuptake inhibitors have been reported to induce anorgasmia both men and women[152,153]; (b) serotonin transporter knockout rats ($SERT^{-/-}$) showed significant elevations of basal extracellular 5-HT levels, which may be considered as a model of anorgasmia[154]; (c) tramadol has been demonstrated to inhibit serotonin reuptake,[79,80] induce hypogonadism (noted to be associated with anorgasmia),[14,149] be useful in treatment of PE,[7] and be an inhibitor to 5-HT_{2C} receptors (orgasm is inhibited by excessive stimulation of 5-HT_{2C} receptors in the spinal cord)[84,155]; and (d) opioids have been reported to delay of orgasm in men.[156]

Findings

The Netherlands Pharmacovigilance Centre Lareb registered 7 reports of anorgasmia associated with the use of tramadol from December 1996 until January 2015 in men.[157] They developed anorgasmia hours to weeks after drug intake. Anorgasmia was associated with ejaculatory failure in 1 patient and ED in another. The dose of tramadol ranged from 50 to 400 mg/day. Drug withdrawal or dose reduction showed recovery in 2 patients. Some of the cases were confirmed by de-challenge and re-challenge testing.

Conclusions

Anorgasmia induced by tramadol has received little attention in literature. To the best of our knowledge, no research effort has been devoted for this adverse effect and its association with tramadol abuse. Well-designed research is awaited.

Risky Sexual Behavior

Rationale

Risky sexual behavior is defined as any behavior that increases the probability of negative consequences associated with sexual contact, including sexually transmitted diseases and unplanned pregnancy. These behaviors are considered in 2 broad categories: (a) indiscriminate behaviors, including having multiple partners; having risky, casual, or unknown partners; and failure to discuss risk topics prior to intercourse; and (b) failure to take protective actions, such as use of condoms and birth control.[158] Two recent systematic reviews and meta-analyses[159,160] found evidence of disproportionately elevated mental health and psychiatric problems (both diagnosis and symptoms) among general population samples who reported nonmedical prescription opioid use. Specifically, the pooled prevalence estimates for any mental health problem was 2 times greater than rates for these problems reported in general populations. Additionally, another meta-analysis[161] suggested that chronic opioid exposure is associated with deficits across a range of different neuropsychological domains. One of these domains is cognitive impulsivity (risk taking or making quick cognitive decisions).

Findings

In a country where recreational drugs abuses are prevalent, Xu et al[19] reported recreational drug use (including tramadol abusers) association with multiple sexual partnerships, unprotected sex, and HIV among Chinese men having sex with men. The authors suggested drug abuse disinhibiting behavior may impair judgment such that safer sex practices are bypassed.[19] The relationship between opioids and HIV appears to be bidirectional; patients with HIV infection are more likely to be prescribed opioids than uninfected individuals.[162] Repeat opioid prescribing may be a marker of advanced HIV disease, more higher-risk sexual behaviors, and prevalent sexually transmitted infections.[163] Another hospital-based case-control study showed that hepatitis C virus infection was detected in 16% of cases.[17] Fortunately, 96% of these cases were abusing tramadol; however, 90% were using more than 1 substance. Moreover, the authors noted significant correlation between psychoticism and criminality subscales in the Eysenck Personality Questionnaire. The second Egyptian study showed high rates of commercial sex work, casual sex partners, and lifetime hepatitis C virus infection, particularly among tramadol users.[18]

Conclusions

From the previous studies, it seems that tramadol might be a risk factor for risky sexual behavior; however, further well-designed studies are awaited particularly from countries where tramadol abuse represents a problem. Future longitudinal studies should focus on the causal and noncausal relationship between tramadol abuse and risky sexual behavior.

FUTURE DIRECTIONS

Globally, the abuse of tramadol has become a primary concern only in the last few years. Concerns over tramadol has dominated the research, policy, and treatment agendas in the Middle East, Africa, parts of Asia, and even in developed countries. Clinical research on drug abuse and sexual function is an emerging field. To date, a small number of studies have been performed, and many of these have been flawed by sampling too few subjects, including patients abusing other substances, examining patients with nonstandardized instruments, following the patients for short period of time, and the poor design of the investigations. As a result, 1 of the obvious recommendations is to target tramadol abuse patients for well-designed clinical research. What are the implications for next steps? First, there is a need to know the size of the problem in the nations that complain about this harm. One rationale for examining tramadol abuse patients, as suggested above, is that there appear to be ethnic differences that affect risk for abuse and addiction and consequently sexual dysfunction or improvement of PE from tramadol use. This can be done in the context of multicenter studies that explore similarities or differences among different ethnic groups to better understand racial/ethnic differences in genetic vulnerability and/or resilience to tramadol abuse and sexual function. Second, replication of findings of tramadol in PE is a critical factor in acceptance of the results. Replication across ethnic groups may represent a particularly powerful confirmation of findings if performed through well-designed studies taking into consideration long-term effects. Third, there is the need to further evaluate the effect of tramadol abuse on erectile function, sexual desire, and testicular functions in the long term with the help of standardized instruments and investigations. Related to this comment is the appropriate selection of the study population. Finally, given the occurrence of anorgasmia with tramadol use relying on the database of the Netherlands Pharmacovigilance Centre, both retrospective and prospective studies could focus on the frequency of occurrence of this adverse effect.

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