

## Gynaecomastia, erectile dysfunction and subfertility from tramadol abuse in a protracted case of left tibiofibula nonunion: A case report

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### Abstract

**Introduction:** The abuse of tramadol is on the increase and has attained epidemic proportion globally. Tramadol, a synthetic opioid is frequently prescribed to manage moderate to severe pain. The aim of this case report is to highlight the possible rare side effects of tramadol abuse in an orthopaedic surgical patient.

**Case report** A 37 year old married school teacher who had left Tibiofibular nonunion resulting from a poorly managed Gustillo-Anderson IIIc tibio-fibular fracture in a road traffic crash about 7 years earlier with associated chronic pain, deformity and limb length inequality for which he started self-medication with tramadol, escalating to 1.5grams per day over the 7 year period. He had two children but his wife had not conceived in the past six years and there was associated poor erection. Examination findings of dysfunctional and insensate foot, tanner stage IV bilateral gynaecomastia and a score of 10 out of 30 on assessment of erectile dysfunction using international index of erectile function (IIEF) questionnaire. Ultrasound report showed normal breast tissues and loss of

normal testicular echotexture, high luteinising hormone level and low testosterone level. His rehabilitation included tramadol withdrawal therapy, below knee amputation and prosthetic fitting. At his six months follow up visit, he had improved IIEF score of 20, his hormonal levels had normalized, and his wife was pregnant.

**Conclusion:** Prolonged use of high doses of tramadol is an uncommon cause of gynaecomastia, erectile dysfunction and subfertility essentially due to testicular atrophy and testosterone suppression. Clinicians should prescribe this medication with caution and adopt multimodal analgesia therapy in management of chronic pain.

**Keywords:** Erectile dysfunction, Gynaecomastia, Sub-fertility, Tramadol abuse.

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### Introduction

Post traumatic and surgical pain management is an important public health concern because approximately 240 million patients undergo major surgery annually worldwide.<sup>1</sup> Postsurgical pain is due to complex response to tissue injury during surgery and also due to secondary inflammatory responses which initiate hypersensitivity of central nervous system receptors to pain signals. Pain after orthopaedic surgeries is usually intense and adequate pain control result in better surgical outcome in terms of overall outcome including patient satisfaction, early mobilization and shorter hospital stay while poorly managed pain causes suffering, interferes with recovery, reduces quality of life and is a major predictor of chronic pain.<sup>2,3</sup>

Opioids are usually prescribed for acute pain as they are classically the mainstay in treatment of surgical pain.<sup>4</sup> However, due to the dangers associated with its abuse, opioid use disorders have become a big challenge in our clinical practice. There are no universally adopted guidelines specific to multimodal pain management after

orthopaedic surgeries which probably would have ameliorated the attendant problems.

The global impact of tramadol abuse liability, dependence and overdose have increased over the years and has led some countries to put tramadol under national drug control.<sup>5</sup> In the latest Narcotic Control Board Survey, tramadol abuse appears to be problematic for 32 countries.<sup>6</sup> In Nigeria, studies have shown that the abuse of tramadol cuts across all geopolitical zones of the country. In Kano, Northern Nigeria a cross sectional study amongst commercial bus drivers reported 83.2% of respondent misuse of tramadol.<sup>7</sup> In Owerri, Southeast Nigeria, a survey of the use of psychoactive substances amongst university students indicated that 53.4% admitted to the use of tramadol.<sup>8</sup>

Tramadol is a centrally acting analgesic with dual mode of action. It acts as an agonist on opioid receptors while inhibiting the serotonin and norepinephrine reuptake enhancing the inhibitory effects on pain transmission in the spinal cord.<sup>9</sup> Its common route of administration is oral though other routes include intramuscular, intravenous, sublingual and rectal suppositories. Following oral administration of the drug, the bioavailability is 66-77% due to first pass metabolism effect and can be improved to nearly 100% through other routes and multiple dosing.<sup>10</sup> It is a commonly used drug in the management of both acute and chronic pain in orthopaedics and trauma as well as in other subspecialties. It is an important choice in patients with

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NSAID-induced gastritis or peptic ulcer disease. The common side-effects has been reported to include headache, dizziness, drowsiness, nervousness, anxiety, feeling of tiredness and suffering, constipation, diarrhea, nausea, vomiting, abdominal pain, itching, sweating, flushing and central nervous stimulation<sup>11</sup>.

Although tramadol has apparently low potential for abuse there has been reported evidence of abuse, addiction and withdrawal syndrome. Thus repeated tramadol administration may lead to accumulation of toxic metabolites, increases the risk of pharmacokinetic interactions and decrease its elimination in the body hence increasing its potential for toxicity.<sup>12,13</sup> These invariably lead to potential side effect on the reproductive systems. Men who chronically use opioids report an unexpectedly high prevalence of erectile dysfunction at younger ages when compared to the general population. Studies have shown that men who chronically abused opioids with mean age of 28-49years have a prevalence of erectile dysfunction which ranges from 21-52%.<sup>14-18</sup>

Gynecomastia is a benign proliferation of glandular tissue of the breast.<sup>19</sup> It has been reported to be idiopathic in 61% of the cases.<sup>20</sup> However some medications have been implicated in the aetiology of gynecomastia. They include anabolic steroids, growth hormones, alcohol and cannabis.<sup>21-24</sup> Tramadol abuse has several health consequences of which gynecomastia, erectile dysfunction and subfertility are possibilities. Reports in literature are sparse. In one series, only 5 (0.6%) of the 786 men with gynaecomastia had tramadol implicated.<sup>25</sup> A search for gynaecomastia from tramadol abuse as a result of orthopaedic postoperative squealae was however not found, hence the need for this case report.

### Case Report

Mr OT was a 37-year-old school teacher who was otherwise normal before being involved in a passenger-motorcycle-RTA about 7 years prior to presentation to our facility. He sustained left tibio-fibular fracture, Gustillo-Anderson type IIIC, with extensive soft tissue injury and partial neurovascular compromise. He was admitted for 6 months at the referral hospital where he had initial resuscitation and wound covered including flap cover and split skin grafting and subsequent open reduction and internal fixation. Patient remembered being placed on several medications including parenteral and oral tramadol. Following discharge from hospital, he could not bear weight on the affected limb which was painful, unstable and differentially shorter. He started self-medication with tramadol initially with a dose of 150mg in three divided doses and gradually progressed to 1.5gm daily over the 7 year period. While on tramadol, it numbed his pain, removed his mind from the affected limb, gave him feeling of highness and temporary detachment from reality. There was no history of alcohol

abuse

He was married with two children; the youngest was 5 years old. He also gave a history of progressive bilateral breast enlargement, low sexual desire and difficulty with achieving and sustaining erection for the period under review. Subsequently he had a full clinical assessment of erectile dysfunction for the past four weeks using international index of erectile function (IIEF) questionnaire<sup>26</sup> which revealed a score of 10 points on a 30 point scale.

Musculoskeletal examination revealed a dysfunctional limb with distal tibio-fibular non-united fracture, loss of sensation around the sole of the foot and 5cm shortening. Breast examination showed bilaterally markedly enlarged painless breasts with nipples pointing antero-inferiorly and below the inframammary folds (Tanner stage IV) with no palpable lump or expressible galactorrhoea. Scrotal examination revealed no abnormalities.

Investigation result included x-rays that showed left tibiofibular fracture non-union with failed narrow dynamic compression plate and loose cortical screws as well as osteoporotic distal tibial segment. Breast ultrasound showed bilateral diffuse increase in both glandular and fatty tissues with no mass lesions. Scrotal ultrasound confirmed both testis to be normal in size measuring 3.47x2.42x1.67cm on the left and 3.7x1.67x2.17cm on the right. Both were diffusely hypoechoic with loss of normal homogenous pattern and architecture. The epididymis were also normal with no varicose veins or intra-scrotal fluid collection. Transrectal ultrasound revealed normal prostate with dimension 23x26x28mm and a volume of 9mls and PSA of 1ng/ml. Male hormonal profile revealed normal luteinizing hormone (LH) of 12.24mIU/ml (1.2-12.5) and normal follicular stimulating hormone (FSH) of 9.55mIU/ml (3.2-15.0).

Prolactin was normal; 1.55ng/ml (1-23) while testosterone was markedly reduced; 0.17ng/ml (2.2 – 10.5). Kidney function test, liver function test, complete blood count and blood glucose were essentially normal.

A diagnosis of left tibiofibular non-union with insensate left foot and tramadol abuse were made. Tramadol withdrawal therapy was instituted and detoxification phase concluded satisfactorily following psychiatric consults.

Patient was offered left below knee amputation which was done after adequate counselling. He is currently on prosthetic rehabilitation, does not take tramadol anymore and his wife had become pregnant. The hormonal parameters had all normalized at about six months follow up with an improved IIEF score of 20. He has not had any regression of the breast sizes and has been referred to Plastic surgery team for operative management of gynaecomastia.



Figure 1. Showing Tanner stage IV bilateral gynecomastia

### Discussion

Substance abuse and the addictive behavior pattern happen to be a universal phenomenon and is currently regarded as major public health problem<sup>25</sup>. The health and social cost of abuse of any psychoactive substance in most cases reflect the most disturbing morbidity and occasionally mortality. The sequelae of the physical, psychological, social, and economic harm that emanates from abuse tend to affect not only the individual but also the family.

This case report has revealed the untoward side effect of tramadol abuse on the hypothalamic pituitary gonadal axis and on the glandular tissues of the breast. The decrease in testosterone levels in the test result could explain the poor libido, erectile dysfunction and subfertility observed in the index patient. This was validated from the abnormal score of 10 he had when assessed using international index of erectile function which depicts that a score less than 14 out of 30 should be referred to a specialist for detailed assessment and treatment.<sup>26</sup> It appears that all opioids cause endocrine deficiencies at least to some degree. Opioid medications disrupt the hypothalamic pituitary gonadal axis which exert inhibitory effect on gonadotrophin releasing hormones thus decreasing luteinizing hormones which

causes the testes to produce less testosterone.<sup>27</sup> Testosterone deficiency results in adverse effects such as weight gain, fatigue, depression, and sexual dysfunction. However our findings depicts a high normal LH, normal FSH and low normal Prolactin levels which contradicts the expected opioid effect on the gonadotrophin releasing hormone.<sup>28</sup> A significant proportion of men treated with sustained action opioids, estimated at 5million in the US and Canada are testosterone deficient.<sup>29,30</sup> This may negatively influence sexual function as seen in our patient. This concurs with the findings that long term administration of tramadol induced structural sperm abnormalities and such effect was attributed to spermicidal effect of tramadol.<sup>31,32</sup> A recent study has also reported low sperm density, motility and vitality among male addicts of tramadol.<sup>33</sup>

Drug induced gynecomastia was established in this patient as other possible cause of gynecomastia was ruled out from the requested investigations including the scrotal ultrasound which excluded testicular tumors and the normal size testicular dimension excluded Klinefelters syndrome. The breast ultrasound showed diffuse increase in glandular and fatty tissues with benign features and no discrete masses. This findings support that the balance between androgens and estrogens is an



Fig 2. Showing dyschromic left leg with severe scarring.

important factor in the development of gynecomastia with estradiol promoting breast development and testosterone inhibiting the development of glandular tissue<sup>19</sup> as seen in the patient with deficient testosterone. The psychological gratification the patient has gained as he opined that tramadol numbed his pain, elevated his mood and made him feel good and detached from the reality was attributed to the euphoric effect of tramadol.<sup>34</sup>

**Conclusion:** Prolonged use of high doses of tramadol is an uncommon cause of gynaecomastia, erectile dysfunction and subfertility essentially due to testicular atrophy and testosterone suppression. Clinicians should prescribe this medication with caution. Adopting a multimodal analgesia therapy in management of chronic pain is recommended.

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