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# Zolpidem dependence, abuse and withdrawal: A case report

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Zolpidem, a nonbenzodiazepine hypnotic, binds to the benzodiazepine binding site on the gamma-aminobutyric acid type A (GABA-A) receptors. Many studies have reported efficacy and safety of zolpidem in treatment of insomnia, low abuse, and dependence capability. However, many cases of zolpidem abuse and dependence were reported around the world. This case showed that zolpidem can exert abuse capability, euphoric mood, tolerance, and withdrawal syndrome.

**Key words:** Abuse, Dependence, GABA-A receptor Agonists, GABA-A receptor antagonists, substance withdrawal syndrome.

**How to cite this article:** Heydari M, Isfeedvajani MS. Zolpidem dependence, abuse and withdrawal: A case report. *J Res Med Sci* 2013;18:1006-7.

## INTRODUCTION

Zolpidem, a nonbenzodiazepine hypnotic which binds to the benzodiazepine binding site on the gamma-aminobutyric acid type A (GABA-A) receptors,<sup>[1-12]</sup> was introduced in Europe in 1986,<sup>[1]</sup> then in France in 1987 (Stilnox<sup>®</sup>)<sup>[2]</sup> and in United States of America (USA) in 1993 for treatment of insomnia.<sup>[1-4,6-10,13]</sup> Zolpidem has main clinical characteristics such as its short action and peculiar neuropharmacologic activity.<sup>[1-4,6,11-13]</sup>

Metabolism of zolpidem mediated by human cytochromes P450 (CYP); so that CYP3A4 has a dominant role and CYP2C9, 1A2, 2D6, and 2C19 have a contributory role in decreasing order of importance; but CYP 2A6, 2E1, or 2C8 have no role in zolpidem metabolism.<sup>[5,6]</sup>

Zolpidem has a sedation property without interfering with other benzodiazepine properties linked to other receptor subtypes. Zolpidem has no residual effects and this may be due to its rapid metabolism via CYP3A4 and CYP1A2 isoenzymes and a short elimination half-life.<sup>[1-3,6,8]</sup>

Several studies have reported efficacy and safety of zolpidem, its well-tolerance in adults and elderly during administration<sup>[2-4,6,11]</sup> and minimal risk of abuse or dependence.<sup>[2-4,6,10-11]</sup>

Interestingly, in this case, zolpidem induced euphoric state and gradually cause tolerance, withdrawal syndrome, and led to dose increase.

## CASE REPORT

The patient was 32-year-old jeweler man who had diploma degree was referred to psychiatric clinic because of restlessness, irritability, myalgia, muscle cramps, sweating, palpitation, insomnia, muscle tic, and jump due to withdrawal of daily use of 400 mg zolpidem. He started to use heroin recreationally since 1997 and after 1 year had used it daily in snuff route for 3 years. Then, he was introduced to Narcotics Anonymous (NA) and was abstinent for 6 years. Two years ago, he used Orap (pimozide) and Xanax (alprazolam) to treat tic and simultaneous anxiety, but he discontinued Xanax because of failure to reduce anxiety and insomnia and his physician prescribed 10 mg tablet of zolpidem instead of Xanax. After use of first dose of zolpidem, he experienced euphoric mood of his heroin addiction and reminded heroin use. The next day, to avoid experience of heroin dependency and its induced euphoria, he used 40 tablets of diphenoxylate with zolpidem, but gradually increased dose of zolpidem and diphenoxylate simultaneously so that he used 100 tablets of zolpidem and 120 tablets of diphenoxylate within 6 months. Then, 6 months later, he discontinued diphenoxylate and used 110-140 10 mg tablets of zolpidem (1,100-1,400 mg) until he experienced convulsion with use of 200 10 mg tablets of zolpidem and hospitalized, and after discharge zolpidem was discontinued completely for 1 month but prescribed zolpidem 10 mg/day again after 1 month. Tics were treated completely with zolpidem use but its dosage increased to 1,000 mg/day again and within 6 months decreased to 400 mg/day

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**Received:** 06-12-2012; **Revised:** 10-02-2013; **Accepted:** 25-07-2013

and discontinued completely a few days before attending psychiatric clinic and he had classic symptoms and signs of opioid withdrawal (runny nose, diarrhea, myalgia, irritability, insomnia, and ...). He had no history of physical problems and known diseases and only had a history of tic in past psychiatric history. Two of his cousins were opioid dependent in family history.

## DISCUSSION

Benzodiazepines exert their effects through three subtypes of GABA-A receptors.<sup>[2-4,6-10,12]</sup> Binding to omega 1 ( $\omega_1$ ) subtype has hypnotic and anxiolytic effects and binding to omega 2 ( $\omega_2$ ) receptor has anxiolytic, myorelaxant, respiratory depression, psychomotor dysfunction effects, and anticonvulsant property. Omega 3 ( $\omega_3$ ) subtype has different structure and function and are on glial cells and other cells.<sup>[7]</sup> Zolpidem as an imidazopyridine is not considered a classic benzodiazepine because of lack of diazepine cycle in chemical structure, but its clinical effect is through benzodiazepine receptors and its effect could be blocked by benzodiazepine antagonists such as flumazenil.<sup>[1,7-8]</sup>

It has been reported that zolpidem has low abuse and dependency capability;<sup>[2-4,6,7,9,10,12,13]</sup> however, many cases of zolpidem abuse and dependency were reported in various European countries and USA.<sup>[2-3,6,8-13]</sup> This case showed that zolpidem can exert abuse and dependency capability and in this case it may be through nonbenzodiazepine receptors because with first dose of zolpidem, the patient experienced euphoric mood; and interestingly, he discontinued a potent benzodiazepine such as alprazolam due to lack of euphoria and sedation and used zolpidem instead of it and increased zolpidem dose gradually. After a while, tolerance is induced and with zolpidem dose decrease and its discontinuance withdrawal occurred. According to the patient, he had reminded euphoric mood due to heroin in first use of zolpidem. Thus, despite primary reports of zolpidem safety and minor abuse and dependency capability,<sup>[2-4,6,7,9-13]</sup> recent reports especially this case showed that zolpidem can exert abuse and dependency. It has been reported that zolpidem pharmacodynamics and pharmacokinetics may have a crucial role in cases of zolpidem abuse, dependence, and withdrawal syndrome.<sup>[5,8-10,12,13]</sup> It is suggested that zolpidem might lose its selectivity on GABA-A receptor and exert the

same pharmacological effects as classical benzodiazepines.<sup>[5,10,12]</sup> Also, low zolpidem clearance capacity in elderly and female population might predispose patients to zolpidem dependence.<sup>[5,9]</sup> It has been proposed that possible GABA-A receptor mutations may be a predisposing factor in zolpidem dependency.<sup>[12]</sup>

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Source of Support: Nil, Conflict of Interest: None declared.