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Short Communication

The association between tramadol hydrochloride misuse and other substances use in an adolescent population: Phase I of a prospective survey

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HIGHLIGHTS

- This article examines the relationship between tramadol misuse and substances use.
- Tramadol has the potential to be a gateway drug for substance abuse.
- The prevalence of tramadol misuse was higher than all other substances.

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ABSTRACT

Background: Tramadol hydrochloride is a common prescription pain reliever that is structurally similar to morphine and codeine with its analgesic effects identified as a mu-receptor agonist. Due to its opioid-like stimulant effects, the potential for tramadol misuse is a public health concern. As such, the aim of this investigation is to estimate the prevalence of tramadol misuse in a sample of Iranian adolescents and to assess the relationship between tramadol misuse and other substance use.
Methods: This is the first phase of a prospective survey examining the prevalence of adolescent smoking status, substances use and related factors in Ilam city, Iran. Grade 10 male and female students (n = 2000) were recruited using multistage sampling. Self-administered multiple-choice questionnaires were conducted with data analysed using cross tabulations and logistic regression models.
Results: The prevalence of lifetime tramadol misuse was 4.8% (7.6% males; 1.8% females). Adjusted odds ratios and confidence intervals for lifetime tramadol misusers reporting substance use during the past month were 2.2 (1.1–4.4) for alcohol, 5.0 (1.5–21.9) for cannabis, 8.9 (2.7–29.4) for ecstasy, 0.5 (0.03–7.0) for methamphetamine and 2.3 (0.7–7.4) for opium.
Conclusion: Tramadol could be a related factor or co-factor for adolescent alcohol, cannabis and ecstasy use. We recommend future longitudinal studies to investigate the possible role of tramadol as a gateway drug in the development of substance abuse.

1. Introduction

Tramadol hydrochloride is a relatively common prescription pain reliever that is structurally similar to morphine and codeine with its analgesic effects identified as a mu-receptor agonist. It is hepatically metabolised and acts by blocking the reuptake of norepinephrine and serotonin (Minami, Uezono, & Ueta, 2007). Due to its opioid stimulant effects (Duke, Bigelow, Lanier, & Strain, 2011), the potential for tramadol abuse is an increasing public health concern. However, mounting evidence from diversion and overdose data suggest a growing number of tramadol abusers, particularly in developing countries such as Iran and Iraq (Babalonis, Lofwall, Nuzzo, Siegel, & Walsh, 2013; Dart, Dasgupta, Bailey, & Spiller, 2011; Iravani, Akhgari, Jokar, & Bahmanabadi, 2010; Lafta, 2011; Momtazi & Rawson, 2010; Senay et al., 2003; Spiller et al., 2010; Zabihi et al., 2011). According to the available data from Iran, 55% of people seeking tramadol from a pharmacy were under the age of 18 years, more than 65% reported a history of addiction and more than 57% had at least one indication of existing tramadol dependence (Zabihi et al., 2011).

To date, no publications have reported any direct relationship between tramadol and other substances, however a number of recent studies have shown that tramadol misuse is associated with

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addictive behaviours among adolescents (Karrari, Mehrpour, & Balali-Mood, 2012; Nazarzadeh et al., 2013; Taghaddosinejad et al., 2011). It is also likely that the development of other substance abuse problems following tramadol addiction is largely being underreported as other substance addictions are not considered to be subsequent to tramadol administration, thus diminishing the reports for tramadol abuse complications.

To establish a scientific evidence base and clarify the possible associations between tramadol and other substance use problems, a cross-sectional study is warranted in the first instance to confirm association. As such, the aim of this investigation is to estimate the prevalence of tramadol misuse in a sample of Iranian 10th grade high school students and to assess the direct relationship between tramadol misuse and alcohol, cannabis, ecstasy, methamphetamine (MA) and opium use.

2. Methods

2.1. Sample

This study forms part I of a prospective survey conducted to assess the prevalence and risk factors associated with adolescent smoking habits and substances use in the Ilam province, west of Iran. Participants were male and female 10th grade students who were recruited using multistage sampling techniques from 75 high schools in Ilam city. Sampling procedures were conducted using the school type as the stratum, combined with the number of students in each school, the number of classrooms, city region (north and south) and gender. Sixty high schools were randomly selected across these 75 high schools, containing 120 grade 10 classrooms. All students within 120 classrooms ($n = 2000$ students) were invited to complete the survey.

2.2. Procedure and approvals

The same researchers visited all 120 classrooms to explain the study to the students and to invite them to participate. A self-administered multiple choice questionnaire was handed out to all students who were informed that their information would remain confidential and participation was non-mandatory. In an attempt to achieve maximum response rates whilst also reducing response bias, researchers held induction sessions to explain the study and answer any questions prior to delivery of the surveys. Questionnaires were anonymous and students were specifically instructed not to write any personal information on the surveys that could identify them. This study was approved by the Research Deputy of Ilam University of Medical Sciences and its Ethics Committee in 2012.

2.3. Measures

The questionnaire design including piloting of the variables, variable scales, reliability of responses and validity have been reported in detail elsewhere (Alireza Ayatollahi, Mohammadpoorasl, & Rajaeifard, 2005; Nazarzadeh et al., 2013). In order to identify participants with a suspected history of tramadol lifetime misuse the following two direct questions were used: "Have you ever used tramadol (without considering your use during the last month)?" and "Have you ever seen tramadol?" Individuals who reported in the affirmative to both of these variables were considered as a 'tramadol misuser'. Similar questions were used for the detection of alcohol, cannabis, ecstasy, MA and opium use within the last month. To assess temporality, we used 'during the last month' in questions related to substance use. Smoking status was determined using a valid algorithm as never smoker, experimenter and regular smoker accordingly (Kaplan, Napoles-Springer, Stewart, & Perez-Stable, 2001). General risk taking behaviour was measured according to the Kaplan method (Kaplan et al., 2001) and self-esteem was measured using the validated Rosenberg 10-item questionnaire (Alireza Ayatollahi et al., 2005). Information pertaining to socioeconomic status (SES) was classified based on five indicators around family housing, which was reduced by principal component analysis (PCA) to produce a score that was stratified into three socioeconomic categories being low, middle and high.

2.4. Statistical analyses

A chi-square test (or Fisher's exact test) was used to examine differences in the prevalence of tramadol misuse across other substance use, demographic and psychological characteristics. 95% confidence intervals (CI) for tramadol misuse and substance use prevalence were calculated using the exact method. Binary logistic regression models were used to develop the optimal adjusted model containing both a single multivariable model with all drug types included and tramadol misuse as the dependent variable, with five different sets of multivariable analyses, one for each drug type as a dependent variable and tramadol as independent. All models were adjusted for a set of similar variables (which were selected based on the literature review). A power analysis was performed using PASS version 11. All analyses were conducted using Stata version 11.2.

3. Results

Of 2000 subjects that approached for inclusion, $n = 1894$ people (94.6%) completed the questionnaire with a mean age of 16.3 ± 0.7 years. The prevalence of tramadol lifetime misuse was 4.7% (CI 95%: 3.8 to 5.8%) (for males = 7.6%; CI 95%: 6.0 to 9.4% and for females = 1.8%; CI 95%: 1.0 to 2.8%). Prevalence of alcohol, opium, cannabis, ecstasy and methamphetamine use were 11.1% (CI 95%: 9.1–13.0%), 2.8% (CI 95%: 1.7–3.8%), 3.3% (CI 95%: 2.1–4.4%), 2.7% (CI 95%: 1.6–3.7%), and 2.1% (CI 95%: 1.1–3.0%) respectively, for both genders combined.

A significant increase in the prevalence of tramadol misuse was observed in men with heavier smoking status, smoking of each family member, lower self-esteem, self-harm, risk taking behaviour, peer influence, quarrelling, social activity and all category of substances use. However, amongst women this relationship was only observed in the presence of self-harm, risk taking behaviour, peer influence, quarrelling and all categories of substances use except cannabis and opium (Table 1).

Adjusted odds ratio (OR) for each addictive substance (dependent variable) by tramadol misuse (independent variable) are reported in Table 2. Among adolescents with a lifetime history of tramadol misuse, significant increases in OR were observed with a 2.2-fold increase for being an alcohol user within the last month, 5-fold increase in cannabis use and a 8.9-fold increase in ecstasy use. This association was not significant for MA and opium. Adjusted ORs for each substance reported as an independent factor for tramadol misuse was significant for alcohol (OR: 2.5), cannabis (OR: 4.9) and ecstasy (OR: 5.6).

4. Discussion

This study demonstrates that alcohol, cannabis and ecstasy use in the last month were all associated with lifetime tramadol misuse in a sample of Iranian adolescents.

A number of possibilities exist which may explain this association between tramadol misuse and other substance use problems in adolescences, including: 1) tramadol use increases the propensity of the adolescent to use other substances, 2) the reverse sequence with using other substances can lead to tramadol misuse, 3) common predisposing factors such as family background which increase the propensity to use both tramadol and other drugs, 4) common phenomenon of poly-substance use, and 5) social perceptions amongst youth about prescription medications such as tramadol being safer due to it being prescribed (Lord, Brevard, & Budman, 2011). Other concerning youth-held beliefs around prescription opioids include: it is easier to hide, the effects last