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Pregabalin misuse in methadone maintenance treatment patients in Israel: Prevalence and risk factors

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ABSTRACT

Background: Drug users reportedly abuse pregabalin, and its combination with opiates was related to fatalities. We aimed to estimate the prevalence of pregabalin misuse and risk factors among patients in methadone maintenance treatment (MMT).

Methods: A cross-sectional study included all current MMT patients (n = 300) after excluding 9 with prescriptions, from a large tertiary medical center university-affiliated MMT clinic in Israel. Pregabalin was tested in one of the routine urine tests for other substances in December 2017. Data on urine results and patients' characteristics were retrieved from the patients' records.

Results: Pregabalin was detected among 53 (17.7%) patients. The group had higher depressive symptoms severity score (21-HAM-D) (11.1 ± 8.4 vs. 8.3 ± 7.8, $p = 0.03$), a higher prevalence of sero-positive HIV (13.7% vs. 4.2%, $p = 0.02$), sero-positive hepatitis C (66.7% vs. 50.4%, $p = 0.04$), DSM-IV-TR Axis I psychiatric diagnosis (54.0% vs. 41.7%, $p = 0.03$), and positive urine for opiates (22.6% vs. 8.9%, $p = 0.008$), cannabis (39.6% vs. 4.0 $p < 0.0005$) benzodiazepine (BDZ) (77.4% vs. 18.2%, $p < 0.0005$) and oxycodone (11.3% vs. 0.4%, $p < 0.0005$). Logistic regression found pregabalin group as more likely to be urine positive to BDZ (OR = 12.8 95%CI 5.0–32.5) cannabis (OR = 22.7, 95%CI 6.3–81.6) and oxycodone (OR = 43.9, 95%CI 3.6–541.4), with higher 21-HAM-D scores (OR = 1.1, 95%CI 1.04–1.2) and hepatitis C sera-positive (OR = 4.1, 95% CI 1.5–11.4). Unexpectedly, 13.2% of the pregabalin group had take-home dose privileges, which are rewards to non-drug abusers.

Conclusions: High prevalence of pregabalin misuse among both BDZ abusers and non-abusers and patients with depressive symptoms supports both the inclusion of routine monitoring for pregabalin and intervention in MMT population.

1. Introduction

Pregabalin is a GABA analog that binds to the alpha 2-delta subunit of voltage-dependent calcium channels. It belongs to the gabapentinoid family together with gabapentin. Pregabalin is recognized as efficacious in pathologies, such as epilepsy, neuropathic pain, and anxiety disorders (Ianni et al., 2017), and it is commonly used as an adjunct for the treatment of chronic pain (Bockbrader et al., 2010). The usage of gabapentinoids has increased internationally, from 0.5% in 2007 to 5.5% in 2015 in Ireland (Daly et al., 2018), from 1.2% in 2002 to 3.9% in 2015 in the USA (Johansen, 2018), and by 350% over 5 years in the UK (Spence, 2013). It has also been reported to be used recreationally to produce feelings of relaxation, calmness, and euphoria (including enhancing the euphorigenic effects of opiates) (Elliott et al., 2017).

Based on a recent review by Evoy et al., (2017) the prevalence of pregabalin abuse in the general population is estimated to be about 1.6%, whereas it ranged from 3% to 68% among opioid users. In the USA, the percentage of individuals who used gabapentin and/or pregabalin increased from 1.2% during 2002 to 3.9% during 2015 (Johansen, 2018), based on the Medical Expenditure Panel Survey (MEPS) that is representative of the non-institutionalized population of the USA. The MEPS found gabapentin and/or pregabalin to be most prevalent among individuals who were older, and who had numerous comorbidities, and/or numerous opioid prescriptions and/or a benzodiazepine prescription. According to their 2014–2015 analyses, 11% of the population reported having more than 2 opioid prescriptions or a

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benzodiazepine prescription, and they accounted for 52.6% of gabapentinoid users. An international adverse event database identified 11,940 reports of gabapentinoid abuse between 2004 and 2015, with > 75% reported since 2012. A German review (Bonnet and Scherbaum, 2018) reported that pregabalin abuse is mostly associated with other substance dependencies, primarily opiate dependence and polyvalent drug use. Drug users preferred oral pregabalin to oral gabapentin, citing a faster and stronger euphoria ("liking").

Since its approval for use in the UK in 2004, pregabalin has become more widely prescribed and is increasingly being mentioned or suspected in fatalities (including drug-related deaths) as an added consequence of its potential for abuse (Dworkin and Kirkpatrick, 2005). There has been an increasing trend of pregabalin to act as a contributing factor to fatalities since it first appeared in the UK mortality databases in 2006 (Schifano, 2014). Pregabalin prescriptions were also associated with overdose-caused deaths according to a USA register-based open cohort study of 4501 methadone and buprenorphine maintenance patients between 2005 and 2012 (Abrahamsson et al., 2017).

There are few reports, including few self-report anonymous surveys, of pregabalin use in opiate maintenance treatment, with findings ranging from 4% to 22% (Piralishvili et al., 2013; Baird et al., 2014). Four studies analyzed several urine samples from small patient groups (Heikman et al., 2016; Sundström et al., 2016; McNamara et al., 2015; Grosshans et al., 2013), and one larger study (n = 280) analyzed pregabalin from hair samples (Ianni et al., 2017). There have been no analyses of the prevalence of pregabalin in MMT patients, and none of the earlier studies reported the characteristics of the abusers concerning socio-demographics, addiction history, or psychiatric comorbidity. Objective analyses of the pregabalin misuse rate among methadone maintenance treatment (MMT) patients has become highly relevant given the associated risks, particularly among opioid abusers. Moreover, most MMT clinics, including ours, provide a take-home dose privilege option, and it is not known whether the misuse is present among those trusted patients as well. Our aims in the current study were to evaluate the prevalence, characteristics, and risk factors of pregabalin misusers among our MMT patients.

2. Methods

The study analyses were approved by the medical center's IRB.

2.1. Study population

The Adelson Clinic treats up to 330 patients who meet criteria similar to those of the US Federal Regulations for entering methadone treatment (i.e., DSM-IV-TR criteria of dependence with multiple self-administrations of heroin per day for at least one year). Characterization, demography, and effectiveness of the clinic have been reported elsewhere (Adelson et al., 2018; Peles et al., 2018). All 309 of the patients who were in treatment during December 2017 and who underwent at least one routine urine test were included in the current study. For the analyses, 9 patients with a medical prescription of pregabalin were excluded, leaving 300 patients in the study.

2.2. Urine toxicology

Patients in MMT undergo periodic observed urine tests throughout the entire length of their treatment. For the purposes of this study, pregabalin was determined for each patient in one of the two observed and random urine samples that are routinely taken during one month for the detection of opiates, cocaine metabolite (benzoylecgonine), benzodiazepines, amphetamines, and cannabis by means of enzyme immunoassay systems (DRI® and CEDIA®) (Hawks, 1986). A pregabalin cutoff urine concentration of 50 ng/ml was taken as being positive, and a positive result was defined by at least one of the urine samples testing positive for the substance. Additional non-routine substances, fentanyl with a cutoff urine concentration of 2 ng/ml, oxycodone with a cutoff urine concentration of 100 ng/ml, and methylphenidate with a cutoff urine concentration of 10 ng/ml, were also tested.

2.3. Patient characteristics

Demographic and addiction history details were retrieved from the patients' records, including lifetime psychiatric diagnosis (DSM-IV-TR). Depression was evaluated clinically, and its severity was graded by the 21-item Hamilton Rating Scale for Depression (21-HAM-D: score range 064, ≥18 defined as "depression") (Hamilton, 1960). The Brief Psychiatric Rating Scale (BPRS) was used to evaluate psychosis (score range 0 = no psychosis to 96 = worst) (Overall and Gorham, 1962).

2.4. Statistical analyses

Statistical analyses were done using the SPSS-22 package. Results were compared using the Chi-square or Fisher's exact test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. The logistic regression model for positive urine for pregabalin was used with all variables that were found to be significant ($p < 0.05$) in the univariate analyses, using backward stepwise (conditional). Odds Ratio (OR) and 95% confidence intervals (CI) are presented. Adequacy of the model was determined with the Contingency Hosmer and Lemeshow test (Hosmer and Lemeshow, 1980) (p = 0.4).

3. Results

3.1. Comparison between characteristics of the positive and negative pregabalin groups (Table 1)

Pregabalin was detected among 53(17.7%) of the patients. The pregabalin group did not differ from the non-pregabalin group by gender (p = 1), age at admission to MMT (p = 0.3), duration of opiate usage pre-MMT initiation (p = 0.8), duration in MMT (p = 0.9), years of education (p = 0.3), proportion of Israeli-born (p = 0.3), proportion of living alone (p = 0.9) and of having ever drug injected (p = 0.2). More of them were hepatitis C antibody-positive (66.7% vs. 50.4, p = 0.04), HIV antibody-positive (13.7% vs. 4.2%, p = 0.02), and more had a DSM-IV Axis I psychiatric diagnosis (54% vs. 41.7%, p = 0.03). The mean 21-HAM-D score was significantly higher for the patients who misused pregabalin (11.1 ± 8.4) compared with the non-users (8.3 ± 7.8, p [F = 4.7] 0.03), with no differences in the BPRS results (16.3 ± 12.5 vs. 14.7 ± 10.7, p = 0.4). More of them had no take-home dose privileges (86.8% vs. 30.0%, p < 0.0005).

3.2. Comparison between substance abuse of the positive and negative pregabalin groups (Table 2)

The 53 pregabalin misusers had a significantly higher proportion of any substance use compared to the 247 non-pregabalin misusers (86.8% vs. 29.1%, respectively, p < 0.0005). Specifically, this applied to cannabis abuse (p < 0.0005), benzodiazepine (BDZ) abuse (p < 0.0005) and opiates abuse (p = 0.008), with no significant differences in cocaine abuse (p = 0.2).

The pregabalin compared to the non-pregabalin misusers also had a significantly higher proportion of the non-routine urine monitored substances namely fentanyl (p < 0.0005), oxycodone (p < 0.0005) and methylphenidate (p < 0.0005) respectively.

3.3. Multivariate analyses (Table 3)

Logistic regression (multivariate analyses) found the pregabalin misusers to more likely be BDZ abusers (OR = 12.8, 95% CI 5.0–32.5), cannabis abusers (OR = 22.7, 95% CI 6.3–81.6), hepatitis C sera-