

# Drug-related deaths linked with concomitant use of methadone and benzodiazepines in the period between 2011 and 2015 in the Republic of Macedonia

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## Introduction

Opioid dependence is a complex socio-medical state and a serious problem for the society, linked with a high morbidity and mortality rate (WHO, 2004). Even though several pharmacological agents are available, in the Republic of Macedonia, the maintenance therapy includes methadone (METH) and buprenorphine, with METH being the first agent used in the opioid substitution treatment (OST) and it still remains the main prescribed medication (EMCDDA, 2013). There are indications that alongside with the general decrease in drug seizures between 2009 and 2012 in Republic of Macedonia, there was some shortage in supply, encouraging users to replace heroin with other substances such as METH, benzodiazepines (BZDs) and tramadol (EMCDDA, 2013). Despite the prescription of BZDs for therapeutic purposes, the prevalence of their misuse among OST patients is reported to be high in other countries and is related to severe consequences such as non-fatal and fatal overdoses (EMCDDA, 2015).

The aim of this report is to assess the number and nature of drug-related deaths (DRDs) in the Republic of Macedonia over the period 2011-2015, with the emphasis on death cases involving positive findings for METH and BZDs.

## Materials and methods

All toxicological analyses from autopsies performed at the Institute of Forensic Medicine in Skopje during a 5-year-period were reviewed. Postmortem toxicological

analysis of blood and urine samples was conducted using biochip array technology and fluorescence polarization immunoassay, respectively. Whenever possible, the positive results from the screening were confirmed by gas chromatography-mass spectrometry (GC-MS), after previous sample preparation by ion-exchange solid-phase extraction (SPE). Acid hydrolysis was performed prior to SPE for the urine samples showing positive results for BZDs tested with screening methods. The concentration of ethanol in the samples was determined by headspace gas chromatography-flame ionization detection.

## Results and discussion

The postmortem toxicological analyses were performed on a total of 1251 cases in the 5 year period being reviewed. A total of 89 cases showed positive results for drugs of abuse, whereas combined use of psychoactive substances was noticed in 57 cases (64.05% of all DRDs). Concomitant use of METH and BZDs was implicated in 39 DRDs over the time period studied (43.82% of the total DRDs), with the highest number of fatalities involving their combined use in 2013 (14 cases). The percentage of METH and BZDs DRDs gradually increases starting from 2011, with the highest peak seen in 2012 and 2013 (50% of all DRDs). After that, the percentage declines in 2014, reaching the same level as in 2011. A rise in the trend of DRDs is seen again in 2015. No information on the possible involvement of deceased in OST was available. In all cases analyzed by GC-MS diazepam was the only BZD identified. The presence of ethanol was detected in only 9 cases of all studied DRDs. Other substances (cannabi-

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noids, cocaine, tricyclic antidepressants and opiates) were detected in addition to the combination of METH and BZDs in 16 cases.

The number of deaths in which METH is either the cause of death or a positive toxicological finding has significantly increased (Mijatović et al., 2014). In some studies it has been reported that alcohol and BZDs are most commonly detected concomitants together with METH (Laberke and Bartsch, 2010; Mijatović et al., 2014). Nonetheless, regarding alcohol presence, this was not confirmed in this report where ethanol was detected in only 9 cases of all DRDs. Concomitant use of METH and BZDs was implicated in 43.82% of the total DRDs, with diazepam being the only BZD identified in all analyzed cases by GC-MS, similar to other studies (Iwersen-Bergmann et al., 2014; Mijatović et al. 2014). Furthermore, this correlates with the data from EMCDDA stating that BZDs with a more rapid onset of action (diazepam, alprazolam) appear to be more frequently used by opioid users than those with a slower onset (EMCDDA, 2015). Much of the BZDs misuse consists of self-medication for treatment of psychiatric and mood disorders, alleviation of withdrawal symptoms and increase of the rewarding and reinforcing effects of the opioids (Eiroa-Orosa et al., 2010; EMCDDA, 2015).

The potential for significant morbidity and mortality with METH, either alone or in combination with BZDs, is widely reported (Lee et al., 2014). METH's inhibitory effect on the brain's respiratory center can lead to respiratory depression, hypoventilation and pulmonary edema (Bernard, 2013). It is suggested that  $\mu$ -opioid agonists suppress respiration by acting on the respiratory centers in the brainstem, decreasing the ventilatory response to CO<sub>2</sub> (Pattinson, 2008). In this way, the inspiration is prolonged, while changes in tidal volume can be observed at higher opioid doses (Lalley, 2003). The concurrent use of opioids with BZDs and other central nervous system depressants is considered to be an important element in the mechanism of death (Bernard, 2013). Some authors suggest that BZDs compete with METH for  $\mu$ -opioid receptors, resulting in higher concentrations of METH in acute intoxications with METH and BZDs, while in chronic abuse situations, BZDs inhibit hepatic enzymes that metabolize METH, also leading to increased METH concentrations (Mikolaenko et al., 2002). Moreover, it had been postulated that BZDs may also have effects on signal transduction and second messenger systems involved with  $\mu$ -opioid receptor regulation (Poisnel et al., 2009). Other possibly fatal METH-related effects in the body, such as pulmonary oedema and arrhythmias secondary to QT-interval prolongation must be also borne in mind (Bernard, 2013).

The high frequency of positive findings on METH and BZDs in postmortem analysis of DRDs implies possible METH diversion and widespread availability of BZDs among METH users.

## Conclusion

It is complicated to establish the role of BZDs in DRDs and their misuse has been shown to contribute to morbidity and mortality rate among METH users. Much still needs to be done regarding the monitoring of METH and educating the patients involved in OST about the risks associated with multiple drug use.

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