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The relationship between bupropion and suicide in post-mortem investigations

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ABSTRACT

We reviewed the 33 727 postmortem toxicology investigations performed in Finland over a period of 5 years (2009–2013) and identified those in which the antidepressant bupropion was detected. Cases positive for other antidepressant drugs were reviewed for comparison.

The postmortem toxicological examination included, in all cases, the routine screening and quantification of hundreds of drugs and poisons using quality-controlled methods.

Bupropion was detected in 65 cases. A large proportion of the bupropion-positive deaths resulted from suicide (55%). In fatal poisoning cases found positive for bupropion, the proportion of suicide was even higher (77%). The measured median bupropion postmortem blood concentration (0.69 mg/L) was markedly higher than the normal therapeutic range in plasma in the treatment of depression (up to 0.1 mg/L) and even higher in fatal bupropion poisonings (13 mg/L).

Only 14% of the deceased positive for bupropion were estimated to be drug abusers. However, nearly all of the drug abuse cases were from the last year of the study (2013), indicating a recent increase of the use of bupropion among drug abusers and possibly even abuse of bupropion itself.

Suicide victims positive for bupropion were younger than those who died with other antidepressant drugs in their blood. In addition, the percentage of fatal poisonings among bupropion-positive postmortem cases was higher than among the users of other antidepressant drugs. Suicide was significantly more common among the deceased positive for bupropion than among users of other antidepressant drugs.

An unknown degree of bupropion degradation before the assay and post-mortem redistribution of bupropion may have impacted the measured levels. Nonetheless, all post-mortem concentrations of bupropion were elevated and especially high concentrations were detected in suicides.

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1. Introduction

Bupropion belongs to the chemical class of synthetic cathinones; a group of abused novel psychoactive substances that have gained widespread publicity over the last decade. Synthetic cathinones are structurally related to cathinone, the principal active compound of khat (Fig. 1). In Finland, the most prevalent of the abused synthetic cathinones have been MDPV, α-PVP and methylone (Fig. 1), all of which are currently banned.

Bupropion (Fig. 1) is approved for medicinal use for the treatment of depression and as a smoking cessation aid, which makes its user profile very different from that of the other synthetic cathinones which have no medicinal use. Bupropion (also known as amfebutamone) is marketed under the trade names Zyban, Voxra and Wellbutrin. Besides its main indications, bupropion has been demonstrated to be effective in the treatment of attention-deficit/hyperactivity disorder (ADHD) [1], chronic fatigue [2], and in the treatment of cocaine dependence [3]. It is a weak norepinephrine-dopamine reuptake inhibitor (NDRI) but the complete mechanism of action is still not completely known [4]. Bupropion undergoes extensive hepatic metabolism to three metabolites: hydroxybupropion, threobupropion, and erythrobupropion. Less than 1% of the parent compound is found in urine [5]. It has also been reported that bupropion is quite unstable in stored non-frozen plasma with a degradation half-life of about 11 h (pH 7.4, 37 °C) [6] but it is stable in plasma frozen at -22 °C or -65 °C and survives several freeze/thaw cycles [7].

The typical therapeutic dose of bupropion is 150–300 mg per day. Plasma levels in the treatment of depression are in the range of 0.025–0.1 mg/L. The elimination half-life of the drug in chronic use is 21 ± 9 h. Steady state plasma concentration after the ingestion of

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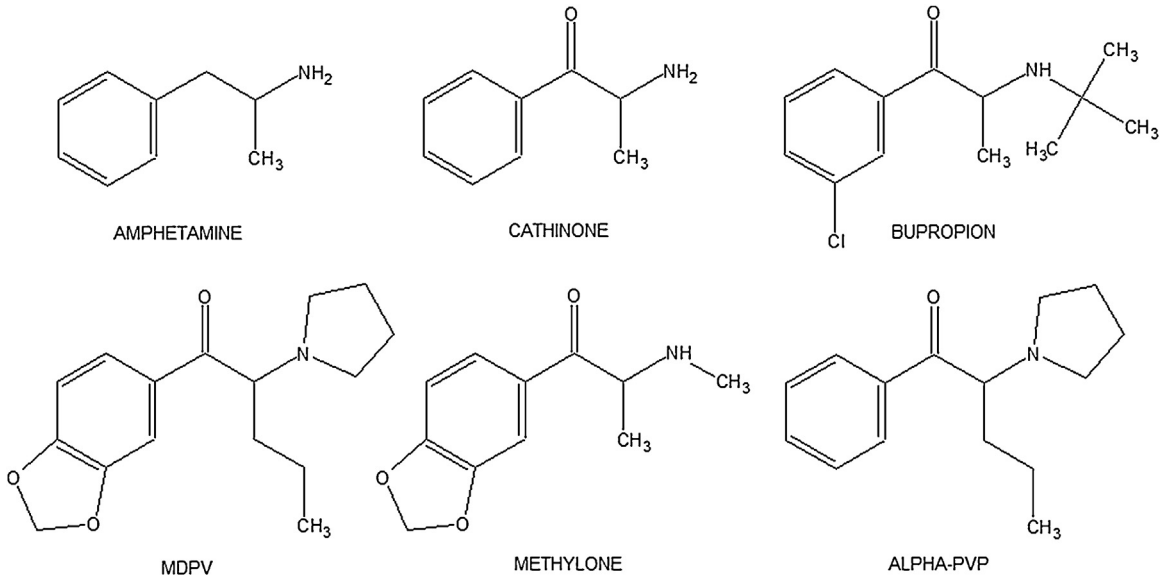

Fig. 1. Chemical structures of amphetamine, cathinone and some of the synthetic cathinones.

therapeutic doses of immediate release products is achieved within 8 days [8,9].

Although originally considered unlikely [10,11], some recent reports of bupropion abuse, especially among young adults and adolescents, have been published. At present, ten peer-reviewed articles in which "bupropion abuse" is mentioned in the title of the article can be found in PubMed (accessed 11 December 2015) [10,12–20]. Half of these articles were published in the last 3 years.

Antidepressant drugs are widely prescribed for the treatment of depression although for many of them the mechanism by which they exert their therapeutic effects is not well understood. The consumption of antidepressants has increased steadily over recent years in many countries and in Finland the consumption in 2013, measured as the number of defined daily doses (DDD) sold by drug wholesalers to pharmacies and hospitals per 1000 inhabitants per day, was above that of the OECD mean (69 vs. 58) [21]. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (www.whocc.no/ddd/definition_and_general_considera/).

The risk of suicide is greatly affected by various biological, psychological, social, and cultural factors. Depression and other mood disorders markedly increase the risk of self-destructive behaviours [22]. Many studies have shown that the class of antidepressant drugs most commonly prescribed for depression in Finland, the selective serotonin re-uptake inhibitors (SSRI), either reduce the risk of suicide [23–25] or at least do not increase the risk of suicide in the first few weeks of treatment, a problem that has been shown for other classes of antidepressants [26].

For individuals abusing drugs, the most common manner of death is generally unintentional (accidental) rather than suicide [27,28]. However, previous studies have suggested an increased prevalence of suicides among deceased positive for synthetic cathinones [29,30]. Additionally, despite its reputation as safe drug [1], in 2004 the US Food and Drug Administration (FDA) issued a public health advisory regarding worsening depression and suicidality in paediatric and adult patients being treated with bupropion and some other newer antidepressants [31]. Further, in 2009 an FDA Post Marketing Review found evidence of suicide and suicidal thoughts among some patients treated with bupropion for smoking cessation [32].

Given these circumstances, we sought to utilize the large registry of forensic toxicology data available in Finland to investigate a possible association between the use of bupropion and suicide. We have reviewed the postmortem cases positive for bupropion in Finland during a 5-year period (2009–2013) in terms of toxicological findings, cause and manner of death, and demographic information. For comparison, we also looked at the suicide rate among those postmortem cases positive for other antidepressant drugs over the same time period.

2. Material and methods

In Finland, all sudden and unexpected deaths are required by law to have a medico-legal investigation, initiated by the police and conducted by a forensic pathologist. According to the law, a medico-legal investigation into the cause of death is to be performed when (1) death is caused or suspected to be caused by crime, injury, suicide, poisoning, occupational disease or medical treatment, or, (2) death has not been caused by a disease, or, (3) during the latest illness the deceased has not been treated by a doctor, or (4) death is otherwise unexpected [33].

As a result of this law, approximately 18–20% of all deceased undergo a medico-legal investigation. In most medico-legal cases, comprehensive postmortem toxicology is also performed. During the study period, the number of postmortem toxicology cases was 33 727, corresponding to about 13% of all deaths.

Autopsies took place on average 6 days after death. Once the cadaver reached the department of forensic medicine it was stored at +4–8 °C but the conditions prior that may have varied considerably depending on the time interval from death to the time when the body was found. Blood samples were collected during the autopsy and stored in tubes contain sodium fluoride as preservative at +5 °C until analysed. The interval between sample collection and analysis was in most cases 1-5 days.

The postmortem toxicological examination included the screening and quantification of hundreds of drugs and poisons by quality-controlled methods. Specifically, bupropion and the other antidepressant drugs were screened in urine by ultra-high performance liquid chromatography coupled with high-resolution time-of-flight mass spectrometry [34,35]. The quantification of the substances in blood was performed using dual-column gas chromatography with nitrogen–phosphorus detections (GC-NPD) [36]. The limit of quantification (LOQ) in blood was 0.10 mg/L for

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