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ORIGINAL ARTICLE

Fatal toxicity index of medicinal drugs based on a comprehensive toxicology database

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Abstract The fatal toxicity index (FTI) is the absolute number of fatal poisonings caused by a particular drug divided by its consumption figure. Consequently, it is a useful measure in evaluating toxicity of the drug and its relevance in fatal poisonings. In this study, we assessed the FTI of medicinal drugs in 3 years (2005, 2009, and 2013) in Finland. As the measure of drug consumption, we used the number of defined daily doses (DDD) per population in each year. There were 70 medicinal drugs in Finland for which the mean FTI expressed as the number of deaths per million DDD over the three study years was higher or equal to 0.1. The Anatomical Therapeutic Chemical (ATC) classification system was used for the classification of the active ingredients of medicinal drugs according to the organ or system which they act on. Of these 70 drugs, 55 drugs (78.6 %) acted on the nervous system (denoted by ATC code N), 11 (15.7 %) on the cardiovascular system (C), three (4.3 %) on the alimentary tract and metabolism (A), and one (1.4 %) on the musculoskeletal system (M). The nervous system drugs consisted of 20 psycholeptics, (ATC code N05), 20 psychoanaleptics (N06), eight analgesics (N02), six antiepileptics (N03), and one other nervous system drug (N07). The highest individual FTIs were associated with the opioids methadone, dextropropoxyphene, oxycodone, tramadol, and morphine; the antipsychotics levomepromazine and chlorprothixene; and the antidepressants doxepin, amitriptyline, trimipramine, and bupropion. Buprenorphine was not included in the study, because most of the fatal buprenorphine poisonings were due to smuggled tablets. A clearly increasing trend in FTI was observed with pregabalin and possibly with bupropion, both drugs emerging as abused substances.

Keywords FTI · Fatal poisonings · Drug sales · Forensic toxicology · Post-mortem

Introduction

Statistics on drug-related deaths are of special interest not only to clinical and forensic scientists but also to drug safety authorities and policymakers. This is due to the fact that post-mortem toxicology using sophisticated analytical technology can produce more solid information on the role of illicit and prescription drugs in poisonings than is obtained from patients within the healthcare system. Comprehensive drug screening, unequivocal identification, and quantitative analysis are an essential part of the performance of post-mortem toxicology laboratories, unlike hospital laboratories that usually rely on a series of rapid immunoassay methods and thus only produce tentative identification [1, 2]. Yet the agents involved in fatal and non-fatal poisonings are largely similar [3]. Information about the type and prevalence of drugs causing fatal poisonings are available from general registers maintained by the national central statistical offices or from special registers, such as those maintained by forensic institutions [4].

In addition to the absolute numbers of fatal poisonings caused by particular drugs, consumption figures of drugs are useful in evaluating their relevance in fatal poisonings. A practical measure of relative drug toxicity is the fatal toxicity index (FTI), which is calculated by relating the number of deaths associated with a given drug to the number of prescriptions for that drug over the same period and area [5–7]. For illicit drugs, fatal toxicity can be evaluated by relating the

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number of associated deaths to measures of availability such as seizures by law enforcement agencies [8]. Several recent studies have been published addressing the FTI for various classes of prescription drugs, such as antidepressants [9–11], sedative-hypnotic drugs [12], carisoprodol [13], and methadone [14, 15]. Drug consumption has been expressed as the number of prescriptions, kilograms, or defined daily doses (DDD) dispensed. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults also including the over-the-counter drugs, and thus the number of DDD is a particularly useful measure of drug consumption [16]. As fatal poisonings more often involve several drugs instead of a single substance, deaths can be classified by all drug findings, by all drugs implicated in the death, or by the most important finding [14]. In Finland, the forensic pathologist in charge of post-mortem cause-of-death investigation needs to define in the death certificate the most important drug finding of a fatal poisoning.

FTI as its many variants has proved to be a feasible tool for assessing the relative toxicity of drugs in overdose. However, the published studies have focused on specific drug categories, especially antidepressants, and have been based on various research methods within different medicolegal systems. There are no studies available aiming to establish the FTI for a multiplicity of drugs and compare the changes between years, using one comprehensive source of homogeneous data and one study setting.

Our objective was to compare the prevalence of medicinal drugs in major therapeutic categories in fatal poisonings related to their consumption in Finland between three separate years over a 9-year period: 2005, 2009, and 2013. The high post-mortem toxicology rate and comprehensive-accredited laboratory investigation produce extensive data on fatal poisonings. As a slightly different array of medicines was on sale each study year, we concentrate on those substances repeatedly implicated in fatal poisonings.

Materials and methods

The laboratory post-mortem database included a forensic pathologist's referral, laboratory analysis results, and information from the death certificate issued by a forensic pathologist. The referral contained background information from the police, such as a brief description of the circumstances of death, known medications, and the main autopsy findings. The analytical data contained analysis results for alcohols, medicines, and drugs of abuse and occasionally for other substances. Information from the final death certificate included the age and gender of the deceased, the cause of death with contributing factors according to the International Classification of Diseases (ICD-10), and the manner of death according to the World Health Organization. The manner of death in fatal poisonings was accident, suicide, or unknown. In medicinal drug poisonings, the principal drug finding indicated in the death certificate was used as the basis to classify a fatal poisoning case. Due to the structure of the death certificate, the present results are based on this most important single drug finding in each case instead of all drugs implicated in the death.

Drug consumption data, including hospital consumption, were obtained from the Finnish Medicines Agency (FIMEA), expressed as defined daily doses (DDD) per 1000 inhabitants per day (DDD/1000 inh/day). Data on fatal poisonings were obtained from the laboratory post-mortem database. The FTI was calculated by dividing the number of fatal poisonings attributed to a certain drug by the consumption of the drug over the same period. For example, there were six fatal metoprolol poisonings in Finland during 2005 (0.11 poisonings per 100,000 inhabitants), and the consumption of metoprolol in 2005, measured as the number of DDD in the whole population, was 44,274,057. This resulted in an FTI of 0.14 deaths per million DDD for metoprolol. Only those drugs were included for which at least one fatal poisoning was recorded in at least two of the three study years. Drugs with considerable illicit trafficking were omitted from the study as the consumption of these drugs could not be assessed using the present method.

The FTI for each studied drug was calculated both for the individual study years (2005, 2009, and 2013) and as a sum of all three years.

Results

The number of post-mortem toxicology cases investigated in Finland in years 2005, 2009, and 2013 was 6210, 6892, and 6568, respectively, and these numbers represented 13.0, 13.8, and 12.8 % of all deaths in each year, respectively. The number of fatal drug poisonings (illegal and medicinal) was 501, 636, and 476, respectively.

Table 1 shows the mean FTIs expressed as the number of deaths per million DDD over the three study years for those 70 medicinal drugs in the descending order for which the FTI is higher or equal to 0.1. Each fatal poisoning was categorized by the most important drug finding associated with the death as stated by the forensic pathologist in the death certificate. The Anatomical Therapeutic Chemical (ATC) classification system was used for the classification of the active ingredients of medicinal drugs according to the organ or system which they act on. Of the 70 drugs, 55 drugs (78.6 %) acted on the nervous system (N), 11 (15.7 %) on the cardiovascular system (C), three (4.3 %) on the alimentary tract and metabolism (A), and one (1.4 %) on the musculoskeletal system (M). The nervous system drugs consisted of 20 psycholeptics (N05), 20

Table 1 Mean fatal toxicity index (FTI) and manner of death from 2005, 2009, and 2013 in Finland for 70 medicinal drugs according to descending order of FTI

		Total deaths	Total sales	Mean FTI	Manner of death		
			DDD	(Deaths/10^6 DDD)	Suicide (%)	Unknown (%)	Accident (%)
N07BC02	Methadone	32	750,333	42.65	0	6	94
N02AC04	Dextropropoxyphene	27	847,894	31.84	56	4	37
N05AA02	Levomepromazine	79	3,604,456	21.92	48	15	37
N06AA12	Doxepin	61	4,359,963	13.99	57	25	18
N05AF03	Chlorprothixene	22	3,095,410	7.11	41	32	27
N02AA05	Oxycodone	51	7,542,630	6.76	35	12	51
N06AA09	Amitriptyline	106	16,216,626	6.54	58	18	25
N06AA06	Trimipramine	7	1,107,592	6.32	43	14	43
N02AX02	Tramadol	96	16,886,539	5.69	39	15	47
N02AA01	Morphine	8	1,527,852	5.24	38	0	63
N06AX12	Bupropion	14	3,210,318	4.36	93	0	7
N05AL01	Sulpiride	2	428,758	4.66	0	100	0
N06AA04	Clomipramine	6	1,385,030	4.33	17	67	17
C07AA05	Propranolol	44	11,491,298	3.83	91	5	5
N05AH04	Quetiapine	56	22,267,205	2.51	86	9	5
N06AX05	Trazodone	2	820,214	2.44	100	0	0
N02AB03	Fentanyl	16	7,799,630	2.05	0	13	88
N05AA01	Chlorpromazine	3	1,513,916	1.98	33	33	33
N02AA59	Codeine[a]	113	57,346,321	1.97	38	20	42
N03AX16	Pregabalin	39	20,299,971	1.92	18	23	59
N06AX18	Reboxetine	1	524,657	1.91	0	0	100
N06AB08	Fluvoxamine	4	2,277,310	1.76	100	0	0
N06AA10	Nortriptyline	3	1,747,041	1.72	33	33	33
N06AX03	Mianserin	6	3,718,824	1.61	17	0	83
N05AH02	Clozapine	20	12,673,159	1.58	45	20	35
N06AX16	Venlafaxine	51	40,567,623	1.26	63	20	18
N05BA12	Alprazolam	41	40,340,908	1.02	41	2	56
N06AB05	Paroxetine	16	17,126,500	0.93	25	44	31
N06AG02	Moclobemide	3	3,274,090	0.92	33	67	0
N03AX12	Gabapentin	6	6,579,026	0.91	33	50	17
N03AF01	Carbamazepine	10	11,645,023	0.86	50	30	20
N05AH03	Olanzapine	24	30,079,094	0.80	63	25	13
C01AA05	Digoxin	20	27,148,383	0.74	50	10	20
C01BC04	Flecainide	5	6,874,115	0.73	80	0	20
N05BB01	Hydroxyzine	6	8,682,932	0.69	50	17	33
C08DA01	Verapamil	4	5,806,157	0.69	100	0	0
C07AB04	Acebutolol	3	4,629,967	0.65	100	0	0
N06AX11	Mirtazapine	28	45,645,484	0.61	57	14	29
N03AX09	Lamotrigine	5	9,036,037	0.55	100	0	0
C02CA01	Prazosin	1	1,932,456	0.52	100	0	0
N05CD07	Temazepam	45	87,120,115	0.52	71	11	16
N05CF01	Zopiclone	71	141,258,189	0.50	66	14	20
N06AX21	Duloxetine	5	10,130,365	0.49	60	40	0
N03AE01	Clonazepam	2	5,531,926	0.36	0	50	50
N02BA	Salicylate	5	14,196,273	0.35	40	40	20
N06BC01	Caffeine	1	2,840,800	0.35	100	0	0

Table 1 (continued)

		Total deaths	Total sales	Mean FTI	Manner of death		
			DDD	(Deaths/10^6 DDD)	Suicide (%)	Unknown (%)	Accident (%)
N05CF02	Zolpidem	11	38,111,177	0.29	82	0	18
M03BX02	Tizanidine	3	10,875,377	0.28	67	0	33
N05AF05	Zuclopenthixol	1	3,955,418	0.25	0	100	0
N05AD01	Haloperidol	1	4,074,436	0.25	100	0	0
A10A	Insulins and analogs	39	159,966,644	0.24	74	18	5
N05AB03	Perphenazine	1	4,205,043	0.24	100	0	0
C08DB01	Diltiazem	3	13,269,634	0.23	67	33	0
N02BE01	Paracetamol	29	133,401,723	0.22	34	21	41
N06AB04	Citalopram and escitalopram	31	150,329,960	0.21	61	16	23
N03AG01	Valproic acid	4	20,031,058	0.20	100	0	0
N06AB06	Sertraline	7	35,054,950	0.20	29	14	57
A10BA02	Metformin	32	170,671,697	0.19	28	34	38
N05BA02	Chlordiazepoxide	1	5,785,137	0.17	0	100	0
N05AN	Lithium	1	6,055,199	0.17	0	0	100
A03FA01	Metoclopramide	1	6,103,943	0.16	0	0	100
C07AA07	Sotalol	1	6,140,399	0.16	100	0	0
N05CD02	Nitrazepam	1	6,183,677	0.16	100	0	0
N06BA04	Methylphenidate	1	6,423,566	0.16	0	100	0
N05AX08	Risperidone	2	13,623,381	0.15	100	0	0
N05BA04	Oxazepam	6	41,209,268	0.15	50	33	17
N06AB03	Fluoxetine	4	29,186,025	0.14	50	25	25
C07AB03	Atenolol	3	24,143,785	0.12	67	0	33
C07AB02	Metoprolol	12	118,750,034	0.10	75	8	17
C01DA02	Glyceryl trinitrate	1	9,982,046	0.10	100	0	0

[a] Excluding codeine combinations in cough medicines

psychoanaleptics (N06), eight analgesics (N02), six antiepileptics (N03), and one other nervous system drug (N07).

Additionally, the percentages of suicide, unknown manner of death, and accident for each drug are illustrated in Table 1.

Table 2 shows the FTIs of 56 medicinal drugs in 2005, 2009, and 2013 divided into major pharmacological categories and, within categories, arranged according to the descending order of FTI in 2013. As only those drugs were included for which at least one fatal poisoning was recorded in at least two of the three study years, a total of 40 different drugs associated with less poisoning cases were omitted from the study. Buprenorphine was not included in the study due to a high volume of illicit trafficking.

Discussion

Central nervous system drugs, especially antipsychotics (N05A), antidepressants (N06A), and opioid analgesics (N02A), comprise the majority of the drugs with a high FTI. Table 1 shows that 21 drugs have an average FTI ≥1.0 deaths per million DDD based on six or more deaths over the three study years, which can be attributed to especially high toxicity. The only cardiac drug meeting these criteria is the adrenergic beta-blocking drug propranolol that, interestingly, is also prescribed for psychiatric conditions, e.g., against stage fright. As seen in Table 1, the manner of death is unknown in unexpectedly many cases, which may reflect the fact that forensic pathologists hesitate to define an overdose death as suicide without irrefutable evidence.

Among antipsychotics, our data shows that the major toxic drugs are levomepromazine, chlorprothixene, quetiapine, and clozapine. The high toxicity and the high rate of suicide among the users of the older antipsychotics are quite well known, and these factors probably explain some of our results. Unfortunately, very little data on FTIs of antipsychotic drugs is available in the literature for the comparison of our results [17]. The atypical antipsychotics quetiapine and olanzapine are to be followed carefully as there is evidence of diversion, misuse, and even dependency syndrome following a marked increase in prescribing of these agents [18]. Recently, the off-label prescribing of quetiapine to treat anxiety and insomnia of

Table 2 Fatal toxicity indices (FTI) in 2005, 2009, and 2013 in Finland for 56 medicinal drugs in descending order of FTI in 2013

ATC code		2005				2009				2013			
		Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD	Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD	Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD
Metabolic drugs (A10)													
A10A	Insulins and analogs	12	0.23	41.63	0.29	12	0.22	55.90	0.21	15	0.28	62.44	0.24
A10BA02	Metformin	7	0.13	35.43	0.20	17	0.32	62.91	0.27	8	0.15	72.33	0.11
Cardiac drugs (C01A, C08)													
C08DA01	Verapamil	1	0.02	2.38	0.42	1	0.02	1.86	0.54	2	0.04	1.57	1.27
C08DB01	Diltiazem	1	0.02	6.52	0.15		0.00	4.14	0.00	2	0.04	2.61	0.77
C01AA05	Digoxin	9	0.17	11.45	0.79	6	0.11	8.67	0.69	5	0.09	7.02	0.71
C08CA01	Amlodipine		0.00	45.18	0.00	4	0.07	68.25	0.06	9	0.17	92.34	0.10
C01BC04	Flecainide	1	0.02	1.80	0.55	4	0.07	2.29	1.75		0.00	2.79	0.00
Beta-blocking agents (C07)													
C07AA05	Propranolol	14	0.27	3.66	3.82	23	0.43	3.85	5.98	7	0.13	3.98	1.76
C07AB02	Metoprolol	6	0.11	44.27	0.14	5	0.09	40.47	0.12	1	0.02	34.00	0.03
C07AB07	Bisoprolol	3	0.06	51.06	0.06	3	0.06	68.93	0.04	1	0.02	80.38	0.01
C07AB03	Atenolol	1	0.02	10.90	0.09	2	0.04	7.66	0.26		0.00	5.59	0.00
Antiinflammatory drugs and muscle relaxants (M01, M03)													
M03BX02	Tizanidine		0.00	3.20	0.00	2	0.04	3.65	0.55	1	0.02	4.02	0.25
M01AE01	Ibuprofen	1	0.02	78.36	0.01	1	0.02	94.89	0.01		0.00	99.47	0.00
Analgesics (N02)													
N02AA05	Oxycodone	9	0.17	1.84	4.89	20	0.37	2.64	7.58	22	0.40	3.06	7.18
N02AX02	Tramadol	21	0.40	5.37	3.91	35	0.65	5.61	6.24	40	0.73	5.91	6.77
N02AB03	Fentanyl		0.00	2.92	0.00	6	0.11	2.72	2.21	10	0.18	2.17	4.61
N02AA59	Codeine[a]	45	0.86	18.17	2.48	46	0.86	20.12	2.29	22	0.40	19.06	1.15
N02BE01	Paracetamol	5	0.10	28.97	0.17	7	0.13	46.10	0.15	17	0.31	58.34	0.29
N02AA01	Morphine	1	0.02	0.38	2.61	7	0.13	0.53	13.27		0.00	0.62	0.00
N02BA	Salicylate	1	0.02			4	0.07	9.08	0.44		0.00	5.11	0.00
N02AC04	Dextropropoxyphene	13	0.25	0.63	20.54	13	0.24	0.21	60.50	1	0.02	0.00	
Antiepileptics (N03)													
N03AX16	Pregabalin	1	0.02	1.84	0.54	12	0.22	7.79	1.54	26	0.48	10.66	2.44
N03AF01	Carbamazepine	6	0.11	4.35	1.38	3	0.06	3.83	0.78	1	0.02	3.46	0.29
N03AG01	Valproic acid	1	0.02	5.81	0.17	2	0.04	6.82	0.29	1	0.02	7.40	0.14
N03AX09	Lamotrigine	2	0.04	2.07	0.97	3	0.06	3.18	0.94		0.00	3.78	0.00
N03AX12	Gabapentin	1	0.02	1.92	0.52	5	0.09	1.88	2.67		0.00	2.79	0.00
Antipsychotics (N05A)													
N05AA02	Levomepromazine	38	0.72	1.46	26.06	26	0.49	1.19	21.82	15	0.28	0.96	15.71
N05AF03	Chlorprothixene	11	0.21	1.32	8.31	3	0.06	1.02	2.95	8	0.15	0.76	10.58
N05AL01	Sulpiride	1	0.02	0.17	5.79		0.00	0.14	0.00	1	0.02	0.12	8.38
N05AH04	Quetiapine	11	0.21	4.01	2.74	25	0.47	7.87	3.18	20	0.37	10.39	1.93
N05AH02	Clozapine	5	0.10	3.74	1.34	7	0.13	4.34	1.61	8	0.15	4.60	1.74
N05AH03	Olanzapine	7	0.13	8.29	0.84	9	0.17	10.41	0.86	8	0.15	11.38	0.70
N05AA01	Chlorpromazine	2	0.04	0.75	2.67	1	0.02	0.55	1.83		0.00	0.22	0.00
Anxiolytics (N05B)													
N05BB01	Hydroxyzine		0.00	2.67	0.00	3	0.06	2.79	1.07	3	0.06	3.22	0.93
N05BA12	Alprazolam	13	0.25	14.52	0.90	19	0.36	14.24	1.33	9	0.17	11.58	0.78
N05BA04	Oxazepam	1	0.02	14.75	0.07		0.00	14.16	0.00	5	0.09	12.30	0.41
Hypnotics and sedatives (N05C)													

Table 2 (continued)

ATC code		2005				2009				2013			
		Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD	Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD	Deaths	Deaths /10^5 inhb/year	Sales 10^6 DDD/ year	FTI Deaths/ 10^6 DDD
N05CD07	Temazepam	13	0.25	35.39	0.37	19	0.36	30.12	0.63	13	0.24	21.61	0.60
N05CF01	Zopiclone	30	0.57	51.54	0.58	29	0.54	49.18	0.59	12	0.22	40.53	0.30
N05CF02	Zolpidem	4	0.08	11.72	0.34	4	0.07	13.50	0.30	3	0.06	12.89	0.23
Antidepressants (N06A)													
N06AA12	Doxepin	22	0.42	1.84	11.95	30	0.56	1.52	19.69	9	0.17	0.99	9.05
N06AX12	Bupropion	1	0.02	0.81	1.24		0.00	0.16	0.00	13	0.24	2.25	5.78
N06AA06	Trimipramine	4	0.08	0.56	7.19	2	0.04	0.31	6.40	1	0.02	0.24	4.19
N06AA09	Amitriptyline	46	0.88	4.74	9.71	39	0.73	5.45	7.16	21	0.39	6.03	3.48
N06AX16	Venlafaxine	11	0.21	8.15	1.35	24	0.45	13.73	1.75	16	0.29	18.68	0.86
N06AB05	Paroxetine	6	0.11	6.37	0.94	6	0.11	5.68	1.06	4	0.07	5.07	0.79
N06AX21	Duloxetine		0.00	0.23	0.00	1	0.02	4.73	0.21	4	0.07	5.17	0.77
N06AX11	Mirtazapine	9	0.17	12.10	0.74	16	0.30	16.29	0.98	3	0.06	17.25	0.17
N06AB06	Sertraline	3	0.06	9.69	0.31	2	0.04	11.80	0.17	2	0.04	13.57	0.15
N06AB04	Citalopram and escitalopram	10	0.19	40.02	0.25	14	0.26	55.20	0.25	7	0.13	55.12	0.13
N06AB03	Fluoxetine		0.00	10.65	0.00	3	0.06	9.84	0.30	1	0.02	8.70	0.12
N06AA04	Clomipramine	3	0.06	0.52	5.79	3	0.06	0.45	6.68		0.00	0.42	0.00
N06AA10	Nortriptyline	1	0.02	0.33	3.07	2	0.04	0.63	3.20		0.00	0.80	0.00
N06AB08	Fluvoxamine	1	0.02	0.96	1.04	3	0.06	0.80	3.75		0.00	0.52	0.00
N06AG02	Moclobemide	2	0.04	1.29	1.56	1	0.02	1.11	0.90		0.00	0.88	0.00
N06AX03	Mianserin	3	0.06	1.57	1.91	3	0.06	1.23	2.44		0.00	0.92	0.00
Drugs used in addictive disorders (N07B)													
N07BC02	Methadone	1	0.02	0.10	10.43	20	0.37	0.12	170.65	11	0.20	0.54	20.48

[a] Excluding codeine combinations in cough medicines

drug addicts has been increasing markedly in Finland and other countries [19].

Among antidepressants, the highest relative toxicity based on our data is seen with doxepin, amitriptyline, trimipramine, bupropion, clomipramine, mianserin, and venlafaxine. The present study confirms the earlier findings that the FTIs for the tricyclic antidepressants are significantly higher than those for the selective serotonin reuptake inhibitors (SSRI), while the other antidepressants fall in between [20–22]). Swedish researchers reported FTI values based on DDD but considered only fatal mono-intoxications due to one single drug in their calculations, and consequently their FTI values were lower than here [9]. Bupropion, a cathinone derivative, is currently prescribed both for smoking cessation and depression. As indicated in Table 2, the FTI of bupropion is drastically higher in 2013 compared to the two earlier study years. There are recent reports in the literature concerning bupropion abuse [23], but it is not yet known if the increase of FTI in our material is due to emerging bupropion abuse or other reasons.

Among opioid analgesics, methadone, dextropropoxyphene, oxycodone, tramadol, morphine, fentanyl, and codeine are the drugs with the highest FTI. The strong opioids methadone, oxycodone, morphine, and fentanyl involve much abuse resulting in unintentional deaths, while the manner of death for the weak opioids dextropropoxyphene, tramadol, and codeine is often more difficult to establish. Buprenorphine, one of the most important drugs that had caused fatal poisonings in Finland, is not included in the present study, because most of the fatal buprenorphine poisonings were due to smuggled tablets [24]. Methadone is predominantly used in opioid maintenance treatment, and the drug is associated with a substantial amount of abuse and diversion. However, the insignificance of its illicit trafficking allows us to include methadone in this study. The FTI of methadone, although showing large variation between the study years, compares well with the essentially similar OD4 score reported to be 20–63 in Victoria, Australia, during 1990–2005 [15]. Dextropropoxyphene is one of the few drugs that have been recalled from the market due to abuse and

excessive overdose deaths—only to be replaced by another problematic drug, tramadol.

Two sedative drugs, pregabalin and alprazolam, stand out in our study by having caused fatal poisonings especially in combination with opioids. Pregabalin is used in the treatment of neuropathic pain and epilepsy, as well as in generalized anxiety disorder. The drug has a steadily increasing FTI during the study years. This is obviously due to the fact that pregabalin with high doses produces benzodiazepine-like effects and thus possesses considerable abuse potential as such or as an opioid booster [25]. Alprazolam is the benzodiazepine with a high abuse liability [26], and it shows the highest FTI of all benzodiazepines in our material. Swedish researchers published FTI values for sedative and hypnotic drugs based either on fatal mono-intoxications or multi-drug intoxications [12]. The former values were understandably always lower than in our study but the latter were fairly similar to ours, e.g., for zopiclone (0.79), zolpidem (0.52), and alprazolam (0.52).

The changes observed in the number of fatal intoxications caused by a certain drug in the study period mainly followed the changes in the sales of the drug (Table 2). It could be hypothesized that if the FTI for an individual drug remained similar between the years, the result would represent an accurate measure of the relative toxicity of this substance. Our data roughly supports this hypothesis as the typical antipsychotics, tricyclic antidepressants, and opioids rank steadily high, followed by atypical antipsychotics and other antidepressants, while sedative-hypnotics, anxiolytics, antiepileptics, and SSRI drugs had somewhat lower FTIs. However, prescription practices, abuse potential, and the patient's perception of toxicity associated with a drug play a major role, and the FTI may change in time as can be seen with pregabalin and possibly with bupropion.

There are some limitations in this study. Most fatal poisonings are caused by multiple drugs taken simultaneously, while the present results are based on the most important single drug finding in each case. The contribution of other drugs present in these poisoning cases could not be taken into account. Occasionally, it can be challenging for the forensic pathologist to point out a single substance as the underlying cause of death. The number of cases attributed to certain drugs listed in the tables is too low to draw statistically significant conclusions. The fatal poisonings due to citalopram and escitalopram could not be differentiated in the present material. Finally, the sales figures of cough medicines (syrups) containing codeine were not available to us.

Conclusions

Instead of simply calculating the absolute numbers of poisoning deaths, the FTI measures relative toxicity and ranks various medicinal drugs according to their lethality. This information helps forensic toxicologists and pathologists in interpreting drug findings in the cause-of-death investigation. In addition, policymakers can exploit the FTI in monitoring the lethality of medicinal drugs in time and detect possible trends that require intervention. The number of DDD is a particularly useful measure of drug consumption, and these figures are usually readily available. The present study has determined the FTI for a larger set of different drugs than has been reported earlier.

Compliance with ethical standards The study was conducted in accordance with all applicable local and international laws and regulations. For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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