# Interactions between tramadol and selective serotonin reuptake inhibitors anti-depressants in post-mortem cases

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## Introduction

**Serotonin** (5-hydroxytryptamine, 5-HT) is a neurotransmitter with receptors in the nervous system and is responsible for a large range of functions, include the regulation of mood and behavior, thermoregulation, attention, appetite and sleep. Serotoninergic drugs act by modulation of the serotonin levels through inhibition of serotonin reuptake, metabolism, synthesis, release, and serotonin receptor activity [1].

**Serotonin syndrome** occurs as a result of excess serotonin at the 5-HT receptor, classically a drug induced disorder characterized by change in mental status (agitation, anxiety, hypomania, and confusion), autonomic hyperactivity (hyperreflexia, tachycardia and diaphoresis), and neuromuscular hyperactivity (hyperreflexia, clonus, myoclonus, tremor and rigidity) and can be lethal. Some antidepressants, antipsychotics, opiate analgesics and antibiotics have been associated with serotonin syndrome [1-5].

**Tramadol** is very often prescribed for pain management in patients with depression in treatment with selective serotonin reuptake inhibitors (SSRI). Serotonergic antidepressants and its concomitant use with tramadol can lead to a drug–drug interaction, resulting in a decrease in the tramadol analgesic effect and a higher risk of serotonin syndrome. These interactions can also change the post-mortem concentrations of the therapeutic drugs and its metabolites, increasing the difficulty in the interpretation of forensic toxicology results, mainly when the concentrations are higher than the therapeutic level [1,3,4].

The **aim** of this study was to review a five-year period of post-mortem cases, in order to examine the prevalence of concomitant use of tramadol and SSRI and the influence in the concentrations found.

## Methods

1122 post-mortem blood samples positive for tramadol, citalopram, fluoxetine, fluvoxamine, sertraline, paroxetine and venlafaxine were selected among all the cases analyzed between 2013 and 2017 in the Laboratory of Forensic Chemistry and Toxicology of South Branch of National Institute of Legal Medicine in Portugal.

The blood samples were prepared using solid phase extraction with OASIS® HLB basic extraction procedure and analyzed with a GC-MS method fully validated for the detection and quantitation of more than 50 drugs.

The quantitative results were listed and metabolic ratios were calculated in tramadol cases with and without SSRI and compared.

| | case | age | gender | TMD | NDT | ODT | SSRI | metab | other substances present | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|
| Citalopram | C 1 | 71 | M | 163 | na | na | 229 | nd | benzos, trazodone, EtOh | suicide/suffocation |
| | C 2 | 82 | F | 344 | 33 | 36 | 314 | nd | bromazepam, ticlopidine | accident/traumatic |
| | C 3 | 53 | F | 94 | 89 | <10 | 395 | nd | fluoxetine, benzos | homicide/traumatic |
| | C 4 | unk | F | 292 | 68 | 99 | 190 | nd | bromazepam | accident/suffocation |
| | C 5 | 41 | F | 770 | 35 | 43 | 2947 | 126 | benzos, amitriptiline | intoxication |
| | C 6 | unk | F | 714 | 250 | 101 | 455 | 185 | codeine | natural |
| | C 7 | 38 | F | 227 | <50 | <50 | <50 | nd | nd | unknown |
| | C 8 | 77 | M | 172 | 113 | nd | 336 | nd | desalquilflurazepam | unknown |
| | C 9 | 55 | F | 691 | 85 | 387 | 38 | 123 | benzos, lidocaine, corticoide | unknown |
| | C 10 | 84 | F | 954 | 31 | 36 | 221 | nd | benzos, mianserine, pethidine, lidocaine | accident/traumatic |
| | C 11 | 82 | M | 2455 | 152 | 117 | 197 | nd | midazolam, lidocaine, paracetamol | natural |
| Fluoxetine | F1 | unk | F | 99 | 390 | 39 | 677 | na | benzos | suicide/traumatic |
| | F2 | 53 | F | 94 | 89 | 25 | 678 | na | citalopram, benzos | homicide/traumatic |
| | F3 | 37 | F | 669 | 473 | 47 | 1148 | na | benzos, topiramate | natural |
| | F4 | 61 | F | 4205 | 3863 | 212 | 1507 | na | benzos, ciamemazine, topiramato | unknown |
| | F5 | 42 | F | 598 | nd | nd | 2149 | 2284 | COHb, benzos, quetiapine | CO intoxication |
| | F6 | 80 | M | 674 | nd | nd | 423 | nd | mirtazapine | natural |
| | F7 | 63 | M | 2816 | 88 | 41 | 102 | nd | benzos, mirtazapine | accident/traumatic |
| | F8 | 65 | F | 15 | 848 | 69 | 367 | 218 | benzos, amitriptiline, levomepromazine | suicide/traumatic |
| | F9 | 84 | F | nd | 709 | 50 | 495 | 211 | carbamazepine | suicide/suffocation |
| | F10 | 77 | M | 94 | 85 | 21 | 66 | 171 | mirtazapine, trazodone | suicide/traumatic |
| | F11 | 56 | F | 619 | 343 | 50 | 8623 | 2496 | EtOH | suicide/intoxication |
| | F12 | 57 | F | 829 | 452 | 76 | 552 | 603 | benzos | unknown |
| | F13 | 83 | F | 648 | 380 | <10 | 713 | nd | nd | unknown |
| | F14 | 67 | M | 147 | 76 | 33 | 115 | 182 | benzos | suicide/traumatic |
| Fluvoxamine | Fv1 | 57 | F | 1400 | 61 | nd | 2187 | na | benzos, trazodone, olanzapine | suicide/intoxication |
| Paroxetine | P1 | 83 | M | 147 | 262 | nd | 160 | na | alprazolam | suicide/suffocation |
| Sertraline | S1 | 68 | F | 93 | 164 | 51 | 522 | 1020 | benzos, mirtazapine | natural |
| | S2 | 87 | F | 618 | 23 | 65 | 108 | 524 | lidocaine | unknown |
| | S3 | 47 | F | 611 | 464 | 69 | 678 | 3083 | benzos, EtOH | suicide/traumatic |
| | S4 | 80 | M | 863 | 26 | 18 | 291 | + | benzos | traumatic |
| | S5 | 56 | M | 116 | 37 | 14 | 454 | + | benzos | suicide/traumatic |
| | S6 | 42 | M | 355 | 151 | 48 | 105 | na | benzos,methadone,olanzapine | natural |
| | S7 | 93 | M | 1992 | 338 | 139 | 1039 | 2417 | nd | suicide/suffocation |
| | S8 | 74 | F | 898 | 3588 | 137 | 117 | 552 | nd | suicide/suffocation |
| | S9 | 41 | M | 881 | 2439 | 460 | 108 | 261 | benzos, AD, morphine, olanzapine, carbamazepine | suicide/intoxication |
| | S10 | 47 | F | 642 | 60 | 203 | 1382 | 376 | benzos, olanzapine | natural |
| | S11 | 37 | M | 3060 | 302 | 890 | 121 | 188 | benzos quetiapine | intoxication |
| | S12 | 78 | F | 535 | 70 | 143 | 2171 | 2093 | paracetamol | unknown |
| | S13 | 88 | F | 907 | 214 | 112 | 232 | 1074 | benzos, morphine, haloperidol, trazodone | unknown |
| | S14 | 81 | F | 2233 | 945 | 934 | 100 | 534 | haloperidol, trazodone | unknown |
| | S15 | 81 | M | 532 | 108 | 116 | 153 | 1414 | nd | accident/traumatic |
| | S16 | 88 | M | 545 | 114 | 151 | 1070 | 3265 | COHb | CO intoxication |
| Venlafaxine | V1 | 70 | F | 463 | 96 | 25 | 655 | 182 | benzos | suicide/intoxication |
| | V2 | 49 | F | 994 | 191 | 208 | 342 | nd | bromazepam, trazodone | accident/traumatic |
| | V3 | unk | M | 1416 | 186 | 50 | 1155 | 86 | EtOH, ciamemazine | intoxication |
| | V4 | 69 | M | 906 | 89 | 182 | 345 | 905 | ticlopidine | natural |
| | V5 | 57 | F | nd | 68 | 17 | 1020 | 1979 | benzos, mianserine | unknown |
| | V6 | 79 | M | 1439 | 2743 | 843 | 2059 | 1475 | nd | unknown |
| | V7 | 86 | F | 1293 | 3987 | 200 | 2731 | 364 | mirtazapine, quetiapine | unknown |

**Table 1.** Tramadol cases that were positive for SSRI, concentrations found (ng/mL) and available information.
Legend: M – Male; F – Female; TMD- concentration of tramadol; NDT – concentration of N-demethyltramadol; ODT– concentration of O-demethyltramadol; SSRI – concentration of the correspondent SSRI; metab – concentration of the main SSRI demethyl metabolite; unk – unknown; na – not analyzed; nd – not detected; + - confirmed but not quantitated; AD – antidepressants; benzos – benzodiazepines; EtOH – ethanol; COHb – CarboxyHemoglobine.

## Results and discussion

More than 20% of tramadol cases were positive to at least one SSRI, mainly sertraline (16 cases), fluoxetine (14 cases) and citalopram (11 cases) (see Fig. 1). More than 9% of SSRI cases were also positive for tramadol. According with reference tables, more than 40% of the combination cases had toxic concentrations for at least one of those compounds. The distribution of the quantitative results for each case is presented in Table 1, together with all the information available.

The concentration ratio between tramadol main metabolites N-demethyltramadol and O-demethyltramadol (NDT/ODT) was generally higher for the cases with SSRI (see Fig 2). NDT/ODT can be useful to evaluate the possible inhibition of CYP2D6 by the SSRI [6]. The influence of tramadol in SSRI concentrations is not very clear yet, and further studies with a larger sample size are needed.

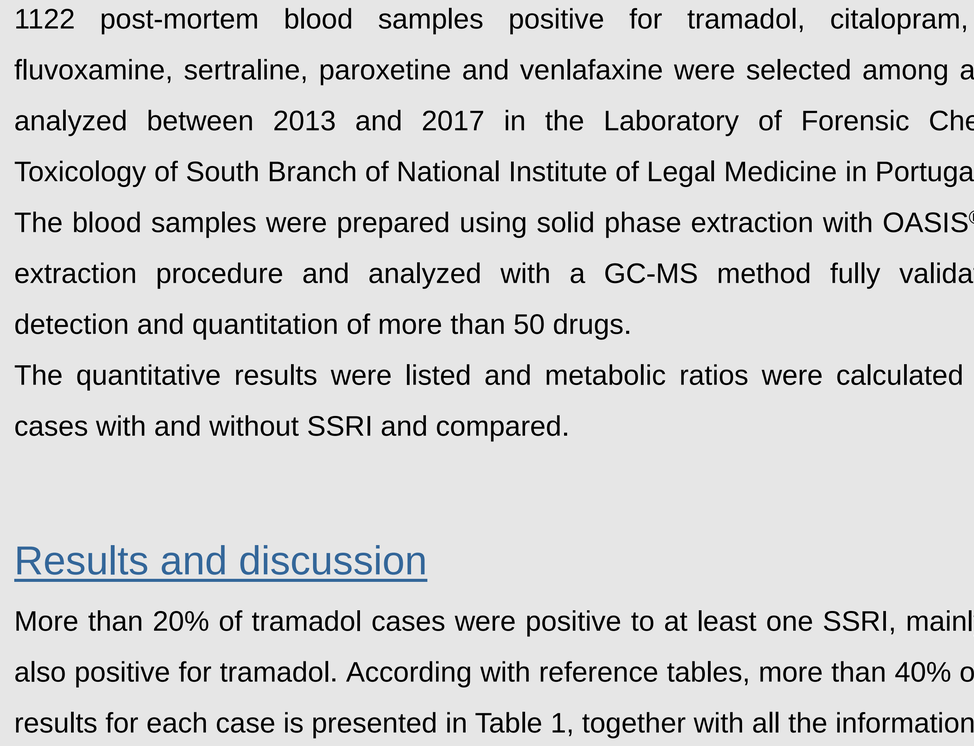


Fig 1. Tramadol cases.

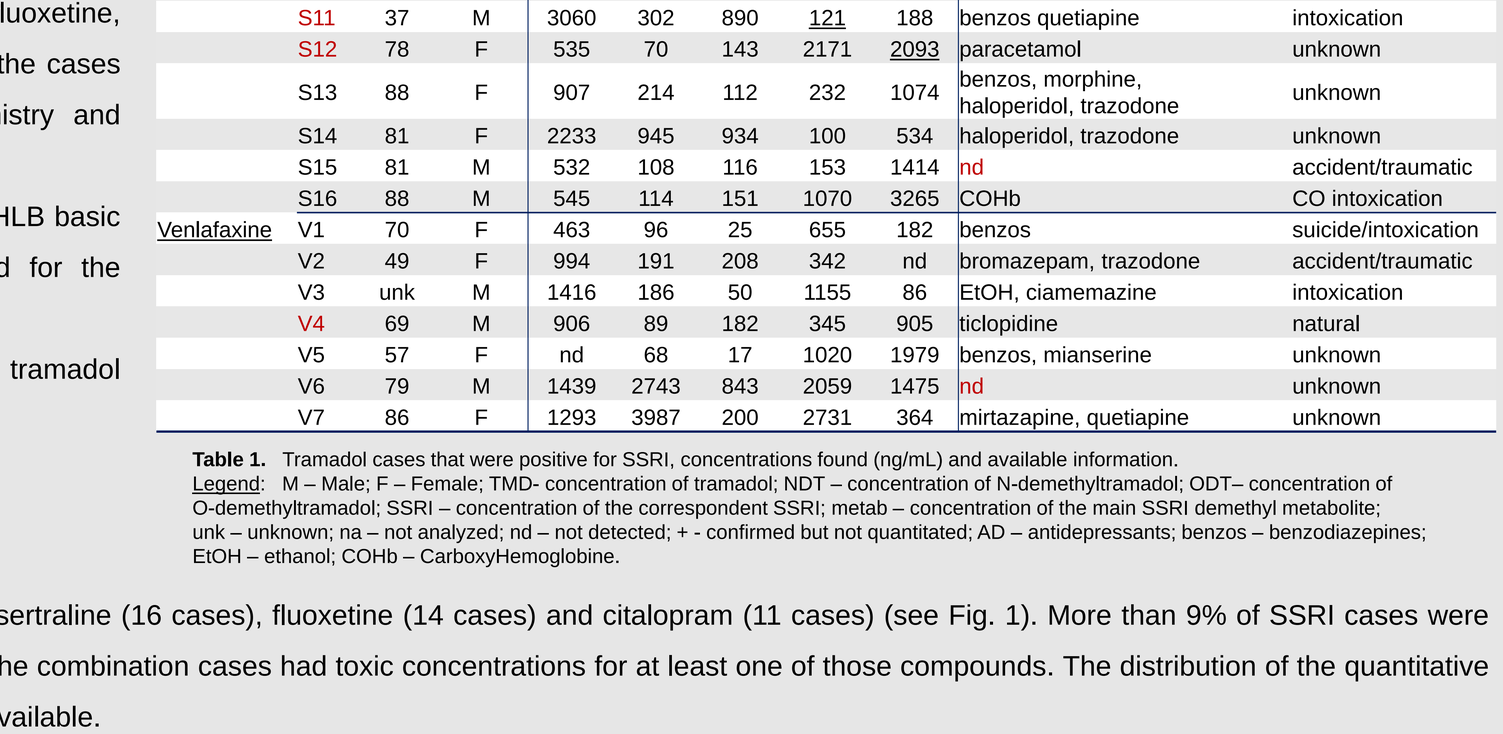


Fig 2. Concentration ratio between N-demethyltramadol and O-demethyltramadol (NDT/ODT) for Tramadol cases also positive for SSRI.

## Conclusions

Drug-drug interactions can be a contributing factor for the cause of death. Data collected suggests that the concomitant use of tramadol and SSRI may influence the tramadol metabolism and change the concentrations in post-mortem blood. The screening of SSRI and metabolites in tramadol cases is important to better understand the forensic toxicology results in post-mortem cases.

References

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