**ONLINE SUPPLEMENTARY MATERIAL**

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1. **Supplementary methods**

**Supplementary table 1.** Criteria for the classification and clinical prioritisation of relevant disproportionality signals

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical priority features for each drug** | **2 points** | **1 point** | **0 points** |
| Number of cases of withdrawal syndrome/Total number of reports of any AE | >10% | 5-10% | 0-4%: |
| Number of cases of withdrawal syndrome without confounders/number of all cases of withdrawal | ≥71% | 51-70% | <50% |
| Significant ROR and IC – consistent across different analyses(in the main analysis, in the intraclass analysis and with methadone as a comparator) | ROR and IC significant in all three analyses | ROR and IC significant in two analyses | ROR and IC significant one analysis |
| Magnitude of the lower limit of the 95% CI of the ROR | .. | >10 | 0-10 |

AEs: adverse events*;* IC: information component; ROR: reporting odds ratio.

Confounders were defined as all drugs that can cause withdrawal syndrome, i.e., other psychotropic drugs, opioids, any other substance of abuse.

# **Supplementary results**

## **Supplementary table 2.** Mean prescribed daily dose for each antidepressant

|  |  |  |
| --- | --- | --- |
| **Drug** | **n of cases with available dose** | **Daily dose (mg/day), median (Q1-Q3)** |
| Amitriptyline | 10 | 50.0 (25.0-75.0) |
| Bupropion | 2 | 150.0 (150.0-150.0) |
| Citalopram | 20 | 20.0 (20.0-40.0) |
| Clomipramine | 24 | 75.0 (36.2-150.0) |
| Doxepin | 3 | 120.0 (110.0-160.0) |
| Duloxetine | 6 | 35.0 (22.5-55.0) |
| Escitalopram | 20 | 17.5 (10.0-20.0) |
| Fluoxetine | 25 | 30.0 (20.0-40.0) |
| Fluvoxamine | 4 | 62.5 (43.7-93.7) |
| Mianserin | 1 | 40.0 |
| Mirtazapine | 6 | 30.0 (18.7-41.2) |
| Paroxetine | 39 | 20.0 (20.0-38.7) |
| Sertraline | 27 | 50.0 (50.0-150.0) |
| Trazodone | 6 | 100.0 (62.5-175.0) |
| Venlafaxine | 35 | 150.0 (75.0-168.8) |

**Supplementary table 3.** Reporting odds ratios (ROR) and information components (IC) for antidepressant-related withdrawal syndrome by class of antidepressant and for each antidepressant using methadone as a positive control

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **n cases** | **n non-cases** | **ROR** | **Lower****95%CI** | **Upper 95%CI** | **IC** | **Lower 95%CI** | **Upper 95%CI** |
| Antidepressants (All) | 379 | 2,817 | 0.07 | 0.06 | 0.10 | -0.42 | -0.59 | -0.30 |
| Tricyclic antidepressants  | 69 | 238 | 0.16 | 0.11 | 0.23 | -0.90 | -1.30 | -0.61 |
| SSRIs | 238 | 2,060 | 0.06 | 0.05 | 0.08 | -0.62 | -0.83 | -0.46 |
| Others | 99 | 620 | 0.09 | 0.06 | 0.12 | -0.99 | -1.32 | -0.75 |
| **Tricyclic antidepressants** |
| Amitriptyline | 14 | 100 | 0.08 | 0.04 | 0.14 | -1.95 | -2.85 | -1.33 |
| Clomipramine | 47 | 117 | 0.22 | 0.14 | 0.34 | -0.82 | -1.30 | -0.47 |
| Doxepin | 5 | 10 | 0.27 | 0.09 | 0.83 | -0.85 | -2.41 | 0.13 |
| **SSRIs** |
| Citalopram | 33 | 307 | 0.06 | 0.04 | 0.09 | -1.78 | -2.36 | -1.37 |
| Escitalopram | 34 | 293 | 0.06 | 0.04 | 0.10 | -1.72 | -2.29 | -1.31 |
| Fluoxetine | 50 | 460 | 0.06 | 0.04 | 0.09 | -1.53 | -2.00 | -1.19 |
| Fluvoxamine | 7 | 33 | 0.11 | 0.05 | 0.27 | -1.67 | -2.97 | -0.82 |
| Paroxetine | 71 | 641 | 0.06 | 0.04 | 0.09 | -1.31 | -1.70 | -1.03 |
| Sertraline | 51 | 378 | 0.07 | 0.05 | 0.11 | -1.42 | -1.89 | -1.09 |
| **Other antidepressants** |
| Bupropion | 6 | 96 | 0.03 | 0.01 | 0.08 | -2.93 | -4.35 | -2.02 |
| Duloxetine | 8 | 84 | 0.05 | 0.02 | 0.11 | -2.46 | -3.67 | -1.66 |
| Mianserin | 4 | 5 | 0.44 | 0.11 | 1.68 | -0.47 | -2.24 | 0.61 |
| Mirtazapine | 10 | 62 | 0.09 | 0.04 | 0.18 | -1.90 | -2.98 | -1.17 |
| Trazodone | 6 | 25 | 0.13 | 0.05 | 0.33 | -1.55 | -2.97 | -0.64 |
| Venlafaxine | 67 | 338 | 0.11 | 0.08 | 0.16 | -1.10 | -1.51 | -0.81 |

CI: confidence/credibility interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio; SSRI: selective serotonin reuptake inhibitors.

**Supplementary table 4.** Disproportionality intraclass analysis for TCAs

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **n cases** | **n non-cases** | **ROR** | **Lower****95%CI** | **Upper 95%CI** | **IC** | **Lower 95%CI** | **Upper 95%CI** |
| Amitriptyline | 14 | 100 | 0.35 | 0.18 | 0.67 | -0.85 | -1.70 | -0.19 |
| Clomipramine | 47 | 117 | 2.21 | 1.25 | 3.89 | 0.35 | -0.09 | 0.73 |
| Doxepin | 5 | 10 | 1.78 | 0.59 | 5.40 | 0.51 | -1.02 | 1.50 |

CI: confidence/credibility interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio; TCA: tricyclic antidepressants.

**Supplementary table 5.** Disproportionality intraclass analysis for SSRIs

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **n cases** | **n non-cases** | **ROR** | **Lower****95%CI** | **Upper 95%CI** | **IC** | **Lower 95%CI** | **Upper 95%CI** |
| Citalopram | 33 | 307 | 0.92 | 0.62 | 1.35 | -0.09 | -0.63 | 0.36 |
| Escitalopram | 34 | 293 | 1.00 | 0.68 | 1.47 | 0.01 | -0.52 | 0.45 |
| Fluoxetine | 50 | 460 | 0.92 | 0.67 | 1.28 | -0.08 | -0.50 | 0.29 |
| Fluvoxamine | 7 | 33 | 1.86 | 0.81 | 4.25 | 0.69 | -0.57 | 1.57 |
| Paroxetine | 71 | 641 | 0.94 | 0.70 | 1.26 | -0.05 | -0.41 | 0.26 |
| Sertraline | 51 | 378 | 1.21 | 0.87 | 1.69 | 0.20 | -0.22 | 0.57 |

CI: confidence/credibility interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio; SSRI: selective serotonin reuptake inhibitors.

**Supplementary table 6.** Disproportionality intraclass analysis for other antidepressants

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **n cases** | **n non-cases** | **ROR** | **Lower****95%CI** | **Upper 95%CI** | **IC** | **Lower 95%CI** | **Upper 95%CI** |
| Bupropion | 6 | 96 | 0.35 | 0.15 | 0.83 | -1.16 | -2.54 | -0.23 |
| Duloxetine | 8 | 84 | 0.56 | 0.26 | 1.20 | -0.63 | -1.80 | 0.20 |
| Mianserin | 4 | 5 | 5.18 | 1.37 | 19.63 | 1.37 | -0.36 | 2.45 |
| Mirtazapine | 10 | 62 | 1.01 | 0.50 | 2.04 | 0.01 | -1.02 | 0.77 |
| Trazodone | 6 | 25 | 1.53 | 0.61 | 3.84 | 0.45 | -0.93 | 1.37 |
| Venlafaxine | 67 | 338 | 1.75 | 1.11 | 2.74 | 0.26 | -0.10 | 0.59 |

CI: confidence/credibility interval; IC: information component; n cases: number of cases of withdrawal syndrome; n non-cases: number of other adverse reactions excluding withdrawal syndrome; ROR: reporting odds ratio.

**Supplementary table 7.** Comparison between serious and non-serious reactions in neonates without psychotropic medications other than antidepressants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Serious reactions** | **Non-serious reactions** | **OR (95%CI)** | **p-value** |
| n | 150 | 8 |  |  |
| Neonatal sex: Females (n) | 52 (34.7)a | 2 (25.0)b | 0.77 (0.07 to 5.60) | 1.00 |
| Neonatal age (days), median (Q1-Q3) | 1.0 (0.0-2.0) | 0.5 (0.0-1.3) | NA | 0.62 |
| Maternal DDD, median (Q1-Q3) | 1.0 (1.0-2.0)c | 1.00 (1.0-2.3)d | NA | 0.71 |
| Duration of the maternal antidepressant treatment (days), median (Q1-Q3) | 266.0 (220.5-277.5)e | NAf | NA | 0.29 |
| Duration of neonatal withdrawal syndrome (days), median (Q1-Q3) | 4.0 (2.0-10.0)g | NAh | NA | 0.86 |

CI: confidence interval; DDD: defined daily dose; NA: not applicable; OR: odds ratio; Q1: first quartile; Q3: third quartile.

aMissing data for 18 neonates

bMissing data for two neonates

cData available for 87 neonates

dData available for three neonates

eData available for 35 neonates

fData available for only one neonate

gData available for 26 neonates

hData available for two neonates

**Supplementary table 8.** Clinical priorityevaluation and classification of relevant disproportionality signals

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug** | n cases | **CRITERION 1** | **CRITERION 2** | **CRITERION 3** | **CRITERION 4** | **TOTAL SCORE** | **Priority level** |
| n cases /total n AEs | SCORE | n cases without confounders/ n cases | SCORE | Significance across analyses | SCORE | Magnitude of ROR lower 95%CI | SCORE |
| Main | Intraclass | vs. methadone |
| Amitriptyline | 14 | 12.28% | 2 | 0.00% | 0 | 🗸 | x | x | 0 | 2.79 | 0 | **2** |  |
| Bupropion | 6 | 5.88% | 1 | 0.00% | 0 | x | x | x | 0 | 0.95 | 0 | **1** |  |
| Citalopram | 33 | 9.71% | 1 | 42.42% | 0 | 🗸 | x | x | 0 | 2.64 | 0 | **1** |  |
| Clomipramine | 47 | 28.66% | 2 | 23.40% | 0 | 🗸 | x | x | 0 | 10.22 | 1 | **3** |  |
| Doxepin | 5 | 33.33% | 2 | 0.00% | 0 | 🗸 | x | x | 0 | 5.93 | 0 | **2** |  |
| Duloxetine | 8 | 8.70% | 1 | 25.00% | 0 | 🗸 | x | x | 0 | 1.60 | 0 | **1** |  |
| Escitalopram | 34 | 10.40% | 2 | 32.35% | 0 | 🗸 | x | x | 0 | 2.86 | 0 | **2** |  |
| Fluoxetine | 50 | 9.80% | 1 | 36.00% | 0 | 🗸 | x | x | 0 | 2.88 | 0 | **1** |  |
| Fluvoxamine | 7 | 17.50% | 2 | 14.29% | 0 | 🗸 | x | x | 0 | 3.26 | 0 | **2** |  |
| Mianserin | 4 | 44.44% | 2 | 0.00% | 0 | 🗸 | x | x | 0 | 7.45 | 0 | **2** |  |
| Mirtazapine | 10 | 13.89% | 2 | 10.00% | 0 | 🗸 | x | x | 0 | 2.88 | 0 | **2** |  |
| Paroxetine | 71 | 9.97% | 1 | 54.93% | 1 | 🗸 | x | x | 0 | 3.11 | 0 | **2** |  |
| Sertraline | 51 | 11.89% | 2 | 25.49% | 0 | 🗸 | x | x | 0 | 3.58 | 0 | **2** |  |
| Trazodone | 6 | 19.35% | 2 | 16.67% | 0 | 🗸 | x | x | 0 | 3.42 | 0 | **2** |  |
| Venlafaxine | 67 | 16.54% | 2 | 37.31% | 0 | 🗸 | x | x | 0 | 5.50 | 0 | **2** |  |

AEs: adverse events; CI: confidence interval; n cases: number of cases of withdrawal syndrome; total n AEs: number of all adverse events; ROR: reporting odds ratio.

1. **Supplementary references**

WHO. MedDRA Hierarchy 2021. https://[www.meddra.org/how-to-use/basics/hierarchy](http://www.meddra.org/how-to-use/basics/hierarchy) (accessed February 2021)