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PII: S1043-6618(18)31991-1
DOI: https://doi.org/10.1016/j.phrs.2018.12.013
Reference: YPHRS 4105

To appear in: *Pharmacological Research*

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DOI: https://doi.org/10.1016/j.phrs.2018.12.013
Reference: YPHRS 4105

To appear in: *Pharmacological Research*

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To appear in: *Pharmacological Research*

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To appear in: *Pharmacological Research*

Received date: 12 December 2018

Please cite this article as: Carnovale C, Gentili M, Viganò C, Carnaghi G, Beltrami M, Bosi M, Analysis of tolerance to antidepressant drug treatment in FDA Adverse Event Reporting System, *Pharmacological Research* (2018), https://doi.org/10.1016/j.phrs.2018.12.013

Analysis of tolerance to antidepressant drug treatment in FDA Adverse Event Reporting System

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Key words
Drug tolerance, antidepressant drugs, major depressive disorder.

Sir,

We read with interest the review by Dr Fornaro and coworkers referring to the loss of efficacy of antidepressant drugs in patients with major depressive disorder (MDD) [1]. We agree that this is an issue of extreme importance from a pharmacological and clinical point of view.

In line with these considerations and in order to characterise further this phenomenon in clinical practice, we believe it may be of interest to report here on our investigation about drug tolerance in patients treated with selective serotonin and serotonin-norepinephrine uptake inhibitors (SSRIs and SNRIs), first-choice agents for the treatment of MDD [2]. This analysis was done on post-marketing data deriving from spontaneous reporting of suspected adverse drug reactions (ADRs) to the FDA Adverse Event Reporting System (FAERS), which represent a useful source of real-world data.

We identified 8.616.488 reports in the period 2004-2015 presenting either an SSRI or an SNRI as the only suspected drug and "major depressive disorder" as indication of the treatment.

We selected 2.923 reports including *tachyphylaxis*, *drug tolerance*, *increased drug tolerance* and *drug inefficacy*. In order to distinguish tolerance occurrence from cases where the drug was shown to be ineffective from the beginning of treatment, in accordance with clinical guidelines [3,4], we set 24 weeks as the cut-off time to differentiate between "drug inefficacy", *i.e.* lack of pharmacological response within 180 days, and "tolerance", defined as an initial response to therapy with subsequent loss of therapeutic response. 806 reports included both the start date of drug administration and the reaction date, which allowed us to accurately evaluate drug inefficacy/tollerance over the period of administration. We identified 490 cases of drug inefficacy (60.79%) and 316 cases of drug tolerance (39.21%). There was no significant difference between male and female patients in terms of drug tolerance rate (34.63% vs 40.88%) and mean treatment duration before tolerance appearance (1143.86 ± 1459.61 vs 1138.23 ± 1319.94 days). We also observed that the SNRIs vs SSRIs showed a significantly higher percentage of drug tolerance (46.37% vs 33.48% p=0.0002). The drug classes also showed a significant difference in terms of time required to develop drug tolerance (1410.45 ± 1546.71 days for SSRIs and 879.28 ± 1080.12 days for SNRIs p=0.0005). Ultimately,

our analysis suggests that, in patients responding to treatment, SSRIs might be more suitable than SNRIs for the long treatment of MDD.

The appraisal of the tolerance phenomenon may yield important insights in relation to the long-term treatment of MDD and achievement of enduring effects of antidepressant drugs. Likewise, prospective randomised controlled trials should be encouraged, as they would yield data as to whether the risk for antidepressant tachyphylaxis is an event common to most treated patients or whether – as Dr Fornaro pointed out - there are specific risk factors and/or clinical and therapeutic issues (also including presence of residual symptoms, serotonergic antidepressant-induced apathy, drug dosage, efficacy/tolerability balance) that might predispose some depressed patients to this condition.

Conflicts of interest

All the authors has seen and approved the submission of this version of the manuscript and takes full responsibility. The authors have no conflicts of Interest to disclose.

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