Archives of Psychiatry and Behavioral Sciences

Volume 1, Issue 1, 2018, PP: 04-06

Utility of Duloxetine Dose-Related Reference Ranges Calculated by AGNP Consensus Guidelines 2017

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Abstract

Updated AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology 2017 list misleading dose-related concentration factors (DRC) for duloxetine. Therefore, calculated dose-related reference ranges of duloxetine were often too low. Future pharmacokinetic studies that strongly control for intrinsic and extrinsic confounding factors that may impact the pharmacokinetics of duloxetine were needed to receive reliable pharmacokinetic data. We propose for the next update two divided duloxetine DRC, for smokers and non-smokers. DRC_{mean} should be approximately 75% higher, for about 0.47 in smokers and 0.75 in non-smokers. Currently, calculated dose-related reference ranges of duloxetine should be applied with caution in clinical practice.

Keywords: *AGNP consensus guidelines, Dose-related reference range, Serum concentration, Therapeutic Drug Monitoring, Duloxetine*

Letter to the Editors

The Therapeutic Drug Monitoring (TDM) task force of the working group on neuropsychopharmacology and pharmacopsychiatry (AGNP) issued in September 2017 updated AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology [1]. Updating the calculation of dose-related reference ranges (DRRR) that were first introduced by Haen and colleagues [2, 3], the guidelines list now dose-related concentration factors (DRC) for 120 drugs, amongst others for the serotonin-norepinephrine reuptake inhibitor duloxetine [1].

Nevertheless, in a small retrospective TDM-analysis (n=9), Hefner and colleagues [4] presented data that indicate similar misleading DRRR of duloxetine, calculated with DRC listed in the updated guidelines [1], compared with the previous guidelines [5]. It was detected that 88.9% (n=8) of duloxetine serum concentrations of "normal", carefully selected non -smokers concerning pharmacokinetic abnormalities were above the calculated DRRR [4]. This result can be justified by the fact that C/D factors of the previous guidelines [5] and DRC of the updated guidelines [1] do not differ markedly (C/D: 0.2-0.57 vs. DRC: 0.28-0.58 ng/mL/mg).

DRC factors in the new guidelines [1] were based on the most evident pharmacokinetic data and compared with the guidelines 2011 [5], two pharmacokinetic studies of Lobo and Tianmei et al. [6, 7] were added additionally to the small study of Skinner and coworkers [8] that comprised only 12 women. These studies suggest, amongst others, a decrease in duloxetine serum concentrations caused by tobacco consumption [6, 7], as smoking induces CYP1A2 [9] and therefore the metabolism of the CYP1A2 substrate duloxetine [10]. Nevertheless, results of Tianmei (n=32 patients) et al. [7] and of the meta-analysis of Lobo and coworkers (n=2002 duloxetine concentrations of 594 patients) [6] did not improve DRC and thus the utility of calculated DRRR in clinical practice [4]. As reviewed by Oliveira et al. [11] numerous limitations have to be considered in such pharmacokinetic studies. So far, no study analyzed pharmacokinetic data of duloxetine in "normal" [1] carefully selected patients

without any pharmacokinetic abnormalities in a naturalistic setting. To increase the utility of DRRR in clinical practice, future prospective pharmacokinetic studies that strongly control for intrinsic and extrinsic confounding factors that may impact the pharmacokinetics of duloxetine, e.g. cigarette-smoke [12], were needed to receive reliable pharmacokinetic data in a naturalistic setting.

In a subanalysis of Hefner and colleagues [4] including "normal" smokers without other pharmacokinetic abnormalities (n=13), 61.5% (n=8) of the measured duloxetine serum concentrations were within and only 15.4% (n=2) below the DRRR 2017, as expected [4]. Providing further pharmacokinetic data in this letter, two-sample t-test indicated no significant differences in duloxetine dosage between smokers and non-smokers ($p>0.05$) and concentration to dose ratio (C/D) was significant lower in smokers (0.47±0.22 ng/mL/mg), compared with non-smokers (0.75±0.17 ng/mL/mg, $p<0.05$). As recommended in the literature [13], a duloxetine dosage of 120mg/d should be aspired in smoking patients. We support and strengthen this recommendation, as smokers, because of a significant lower C/D, need a higher duloxetine dose to reach the therapeutic reference range of 30–120 ng/mL. Nevertheless, only 5 smokers ingested 120mg and 1 patient 180mg duloxetine per day. Therefore, 4 smokers (30.8%) were below the therapeutic reference range of duloxetine. As no area under the concentration curve (AUC) values were available, no new DRC could be calculated, but in relation to these calculated C/D for smokers and non-smokers, we propose for the next consensus update two divided DRC, for smokers and non-smokers. Based on (hopefully) future pharmacokinetic studies, DRC should be for about 0.47 in smokers and 0.75 in non-smokers. Thus, DRC_{mean} of non-smokers should be approximately 75% higher, compared with the current DRC_{mean} of 0.43. As expected, when calculating DRRR with DRC_{low} of 0.6 and DRC_{high} of 0.9, 9 smokers (69.2%) would be below and 6 non-smokers (66.7%) within the DRRR. Furthermore, calculation of DRRR with these recommended DRC and with a recommended exemplary treatment dosage of 90mg leads to clinically more realistic duloxetine serum concentrations of 54-81 ng/mL in non-smokers, compared with the calculated duloxetine concentration of 25,2-52,2 ng/ml in the guidelines 2017 [1].

The DRRR calculation was further ameliorated in the guidelines 2017 [1] and subsequent clinical decision making, but further pharmacokinetic data is needed to allow a better "forecast" of the expected duloxetine drug concentrations in a psychiatric patient. Currently, DRRR of duloxetine should be used with caution and the dosing considerations should be based on the smoking status of the individual patient. Therapeutic drug monitoring should be used to titrate the patient within the therapeutic reference range of duloxetine.

Conflicts of Interests

Gudrun Hefner is a co-author of the new published AGNP Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. She reports no conflict of interest with this publication. All other authors declare no conflicts of interest as well.

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Citation: **G. Hefner, M. Hahn, M. Buenger, S. C. Roll**. *Utility of Duloxetine Dose-Related Reference Ranges Calculated by AGNP Consensus Guidelines 2017. Archives of Psychiatry and Behavioral Sciences. 2018; 1(1): 04-06.*