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Evaluating the dose-dependent mechanism of action of trazodone by estimation of occupancies for different brain neurotransmitter targets

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Trazodone is a drug that was introduced in the clinic almost 40 years ago. It is licensed to treat depression, but it is also commonly used off-label to treat insomnia. A recent study shows that it could be promising in preventing neurodegeneration in mice, and clinical trials to assess its possible beneficial effects of dementia and Alzheimer's disease are expected to start soon in humans. In this study, we describe the dose-dependent pharmacology of trazodone by carrying out pharmacokinetic simulations aiming to predict the brain concentrations of trazodone for different drug dosing regimens and calculating occupancy for 28 different targets for which published trazodone-binding data are available. Our study indicates that low doses of trazodone (typically 50 mg daily) should suffice to block specific receptors responsible for the hypnotic effect and to provide the protective effect against neuroinflammation and neurodegeneration that could be beneficial in dementia. Higher doses are required for an antidepressant effect. The occupancy of specific receptors at therapeutic doses also explains the peculiar side effects reported by patients treated with trazodone (e.g. dry mouth, hypotension, and priapism).

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