# Human pharmacology of current and novel gaba(a)-ergic treatments for anxiety

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*Stellingen behorende tot het proefschrift*

## HUMAN PHARMACOLOGY OF CURRENT AND NOVEL GABA-A-ERGIC TREATMENTS FOR ANXIETY

1 The pharmacological selectivity of novel α2,3-subtype selective GABA(A) receptor partial agonists is demonstrated by their distinct effect profile on the neurophysiological and neuropsychological measurements reflecting the function of multiple CNS-domains, in comparison with benzodiazepines, the non-selective full GABA(A) agonists *(this thesis)*.

2 Normalizing the off-target pharmacodynamic effects against the on-target effect on saccadic peak velocity is a useful approach to present the pharmacological feature of GABA(A)ergic modulators *(this thesis)*.

3 Combination of anxiogenic symptom provocation paradigm with the validated neurophysiological and neuropsychological biomarkers may provide further construct validity for clinical effects of novel anxiolytic agents *(this thesis)*.

4 There is considerable preclinical evidence that the GABAergic system in general and its α2,3 subunit-containing GABA(A) receptor subtypes in particular are implicated in the pathophysiology of anxiety disorders. Nonetheless, the clinical efficacy of selective GABA-A-α2,3-agonists for anxiety disorders has not been unequivocally demonstrated. This could be related to the underestimation of pharmacologically active doses in early drug development *(this thesis)*.

5 Personalised medicine is an interesting concept that assumes individual variability in responsiveness to medicines. However, personalised medicine can only be widely applied if there are sensitive and specific and quantitative measures of this responsiveness in individuals. These are currently lacking in most diseases and clinical pharmacologists are ideally placed to play an important role in the development of such measures (*Cohen AF, email to Xia Chen, Aug 16, 2017*).

6 In the roadmap of novel drug discovery and development, translational medicine seeks to translate biological and molecular knowledge of disease and pharmacological features of a drug into innovative strategies that reduce the cost and increase the speed of delivering new medicines for patients (*adapted from: Bruce Littman & Rajesh Krishma, Translation Medicine and Drug Discovery, 2011; Preface:1*).

7 The essence of rational drug development is to ask important questions and answer them with appropriate studies using fit-for-purpose biomarkers (*Cohen AF et al., Annu Rev Pharmcol Toxicol 2015; 55: 55-74*).

8 Anxiety disorders arise from disruption of the highly interconnected circuits normally serving to process the stream of potentially threatening stimuli. The resultant imbalance in these circuits cause a fundamental misinterpretation of neural sensory information as threatening and leads to the inappropriate emotional- and thereby behavioral-responses seen in anxiety disorders (*adapted from: Calhoon GG & Tye KM. Nat Neurosci. 2015; 18(10): 1394-404.*).

9 Whereof one cannot speak, thereof one must be silent. We should recognize how little is achieved when a specific research problem is solved. (*adapted from Ludwig Wittgenstein, Tractatus Logico-Philosophicus, 1922*)

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