

University of Groningen

The a-typical effects of olanzapine on body weight regulation

Evers, Simon

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2015

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Evers, S. (2015). *The a-typical effects of olanzapine on body weight regulation: And the possible counter effects of topiramate.* [S.l.]: [S.n.].

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

The atypical effects of olanzapine on body weight regulation

and the possible counter effects of topiramate



Colofon:

The research reported in this thesis was carried out at the department of neuroendocrinology of the university of Groningen, the Netherlands and was financially supported by Top Institute Pharma, project T2-105.

Cover illustration by Harm Plat (Harm Plat Art Production). *Front*: The mechanical rat illustrates the connectivity of all physiological systems in the body. *Back*: Olanzapine (top left molecule) and Topiramate (top right molecule) are designed as a set of different gear wheels, representing the capability of acting on a variety of gears (receptors) located throughout the body.

Cover design: Lieke van Gijtenbeek

Printed by: Ipskamps drukkers

ISBN: 978-94-6259-546-0

© by Simon Sjors Evers. No part of this book may be reproduced or transmitted in any form or by any means without prior written permission of the author.



**rijksuniversiteit
 groningen**

The a-typical effects of olanzapine on body weight regulation

and the possible counter effects of topiramate

Proefschrift

ter verkrijging van de graad van doctor aan de
 Rijksuniversiteit Groningen
 op gezag van de
 rector magnificus prof. dr. E. Sterken
 en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

vrijdag 6 maart 2015 om 12.45 uur

door

Simon Sjors Evers

geboren op 12 September 1981
 te Almelo

Promotores:

Prof. dr. A.J.W. Scheurink

Prof. dr. G. van Dijk

Beoordelingscommissie:

Prof. dr. G.J. ter Horst

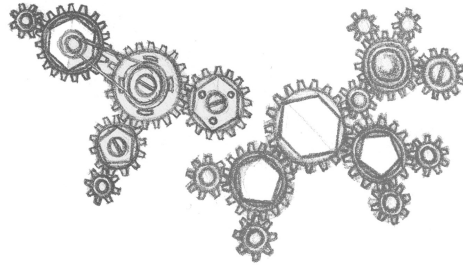
Prof. dr. A. Kalsbeek

Prof. dr. S.C. Woods

Rijksuniversiteit Groningen

Universiteit van Amsterdam

University of Cincinnati



“Erst kommt das fressen, dann kommt die moral.”
Bertholt Brecht (1928), Die Dreigroschenoper.

Table of Contents

Chapter 1: Introduction

How the antipsychotic Olanzapine causes weight gain and insulin resistance and the possibility to suppress this by using Topiramate as an adjunctive treatment 9

Chapter 2: Pharmacokinetics

Topiramate affects pharmacokinetics of Olanzapine in rats, with consequences for glucose and body temperature homeostasis 39

Chapter 3: Gastroenterology

Olanzapine disturbs luminal glucose absorption via inhibition of gastrointestinal motility 63

Chapter 4: Physiology and Behavior

Olanzapine causes hypothermia, inactivity, a deranged feeding pattern and weight gain in female Wistar rats 81

Chapter 5: Reproductive System

Olanzapine disrupts estrous cyclicity in female Wistar rats and induces hyperprolactinemia; a possible cause for weight gain, increased food intake, and insulin desensitization 99

Chapter 6: Psychogenetics

Roman High/Low Avoidance rat selection lines differ in their response to Olanzapine treatment at the level of body weight regulation and mesolimbic cortical mRNA expression 123

Chapter 7: Proteomics

Olanzapine inhibits body weight gain in male Wistar rats, which is amplified by adjunctive Topiramate treatment; hepatic proteome analysis points towards a disruption in growth hormone regulation **165**

Chapter 8: Humans

A low TSH profile predicts Olanzapine-induced weight gain and relief by Topiramate in healthy male volunteers..... **197**

Chapter 9: General Discussion

General discussion **233**

Chapter 10: Nederlandse samenvatting

De a-typische effecten van Olanzapine op gewichtsregulering en de mogelijke tegenwerking van Topiramaat..... **251**

Addendum

Curriculum Vitae **261**

List of Publications **263**

Abstract **265**

Samenvatting **267**

Dankwoord **269**

